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ANATOMIC EVIDENCE OF FUNCTIONAL DISORDERS OF THE HEART

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The pathologist, at postmortem examination, is often confronted with the difficult task of deciding whether or not during life the heart has shown functional disorders, such as valvular insufficiency, stenosis of the valvular orifices or dilatation of the chambers. While the anatomic changes revealed at autopsy are often so pronounced that an abnormality of the physiologic activity of the heart can easily be deduced from the gross findings alone, there are many instances in which it is not possible from the gross or from the histologic changes to draw any definite conclusions as to physiologic disturbances. Between these two extremes, there are a number of cases which reveal certain anatomic changes which, after proper evaluation, may aid in the diagnosis of functional disorders. My purpose in this communication is to relate the results of a study of such intermediate cases and to correlate certain disturbances of the function of the heart which were diagnosed clinically with a number of grossly and histologically recognizable structural changes.

AORTIC INSUFFICIENCY

In a number of cases which were diagnosed clinically as aortic insufficiency, circumscribed whitish areas of endocardial thickening were found on the interventricular septum of the left ventricle. Often such thickenings were seen in the region of the trabeculae carneae where, in the form of fibrous cords, they sometimes bridged some of the trabeculae. More commonly, these thickenings were encountered in the endocardium of the lower third of the left ventricle. In more severe cases, they were found just beneath the aortic cusps. Occasionally, actual endocardial pockets could be found with their openings invariably directed toward the aortic valve. Among ninety-three cases of clinically recognized aortic insufficiency, such pockets were found in fifteen. In some instances, one or several rows of pockets resembling cusps of the aortic valve were found.

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Histologically, the thickened endocardial areas may show either evidence of old inflammatory lesions or simple fibrosis and hyalinization. In a previous communication,[1] it was pointed out that according to the histologic changes these endocardial thickenings might be the result of either a mural endocarditis or a primary mechanical irritation. In the latter instance, it must be assumed that the regurgitating blood and pressure acting as a chronic irritant primarily produce circumscribed fibrosed areas of the endocardium. As soon as irregularities of the endocardium are formed, the continuous regurgitation with formation of eddies in these regions finally results in the formation of pockets.

These pockets have been the subject of much controversy. Zahn [2] considered them as characteristic of aortic insufficiency. Krasso [3] spoke of diastolic pockets to indicate that they were the result of the columns of blood regurgitating during diastole. Ribbert,[4] on the other hand, quoting Lotti, considered a possible congenital genesis for endocardial pockets. He mentioned several instances of circumscribed endocardial thickenings that were not associated with valvular defects, even though in some of his cases a valvular endocarditis existed. As was mentioned before, at autopsy it is often impossible to make a diagnosis of valvular insufficiency. The question naturally must be considered as to whether such findings as Ribbert described were the result of valvular insufficiency rather than a coincidental condition present since birth in hearts which showed evidence of valvular endocarditis even though valvular insufficiency, from examinations of the valves, was not apparent. Ribbert, however, considered an aortic insufficiency also of importance in the formation of these endocardial pockets.

In the present series, whenever endocardial pockets were found, clinical evidence of aortic insufficiency had been present. In several instances in which the clinical diagnosis of aortic insufficiency had not appeared on the patient's record, a check-up of the physical findings revealed the presence of a diastolic murmur over the aortic area and other clinical symptoms which could be interpreted to have been the result of aortic insufficiency. Endocardial pockets open toward the aortic valve were never encountered in normal hearts or in hearts which were the seat of congenital anomalies. From this material there is no reason for the belief that they are the result of a congenital anomaly. Diastolic endocardial pockets (Krasso), in my opinion, are absolute proof of aortic insufficiency.

Circumscribed endocardial thickenings alone, without the formation of endocardial pockets, may be indicative of a healed mural endocarditis

1. Saphir, O.: Am. J. Path. **6**:733, 1930.

2. Zahn, F. W.: Verhandl. d. Kong. f. inn. Med. **13**:351, 1895.

3. Krasso, H.: Frankfurt. Ztschr. f. Path. **37**:136, 1929.

4. Ribbert, H.: Die Erkrankungen des Endokards, in Henke, F., and Lubarsch, O.: Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, Julius Springer, 1924, vol. 2, p. 184.

and therefore cannot be regarded as characteristic of valvular insufficiency. Only if by histologic examination primary inflammation can be ruled out as their cause may a mechanical genesis for their formation be accepted, but this will rarely be the case.

STENOSIS OF THE AORTIC ORIFICE

The recognition of this condition at autopsy is probably easier than that of aortic insufficiency, because of the fact that it is usually caused

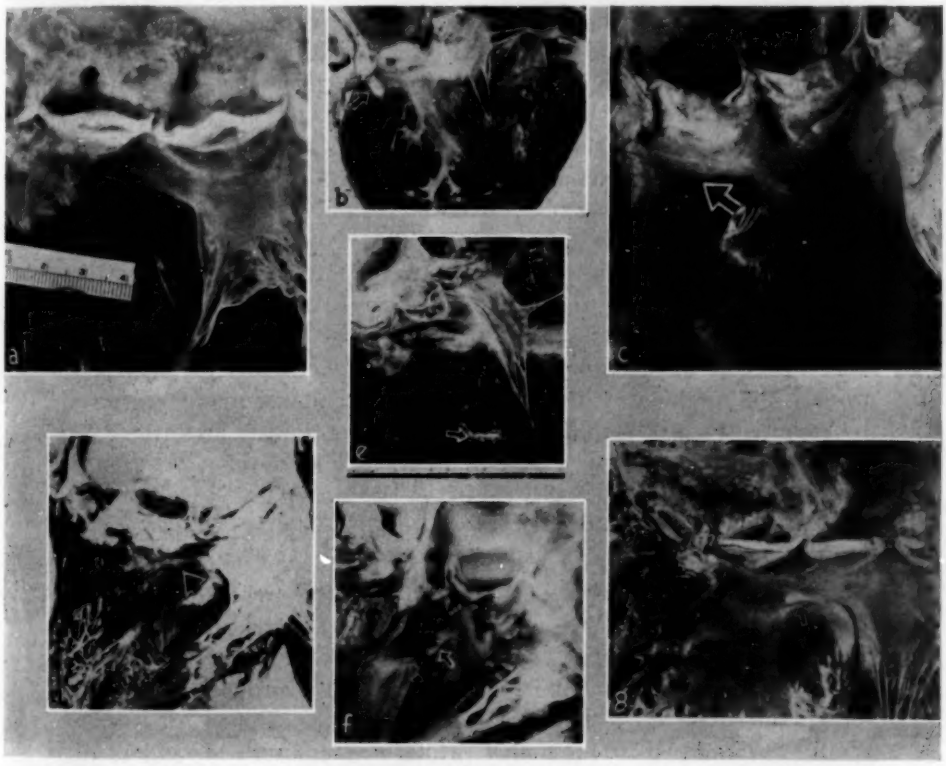

Fig. 1.—Anatomic studies showing: *a*, endocardial thickenings beneath the aortic valve with minute diastolic pockets (syphilitic aortic insufficiency); *b*, circumscribed endocardial thickening (stenosis of the aortic orifice); *c-e*, diastolic pockets (healed endocarditis of the aortic value, with insufficiency); *f*, diastolic pockets (subacute bacterial endocarditis with insufficiency of the aortic valve), and *g*, systolic and diastolic pockets (syphilitic aortitis with insufficiency of the aortic valve, marked hypertrophy and dilatation of the heart, and relative stenosis of the conus aorticus).

by adhesions between the lateral parts of the cusps. Such adhesions, even though they may be slight, are easily recognizable. In several of the cases in the present series, circumscribed areas of endocardial

thickenings were noted just beneath the aortic valve. Occasionally, such regions revealed small openings which were directed toward the apex of the heart. Histologically, these lesions are similar to those seen in cases of aortic insufficiency. Pockets open toward the apex are encountered less frequently than those open toward the aortic valve. In this series, they were found in four of fifty-one cases of stenosis of the aortic orifice. Krasso named the pockets with their opening directed toward the apex of the heart, "systolic pockets," and claimed that they were significant of stenosis of the aortic orifice.

In the present study, systolic pockets were more commonly encountered in hypertrophic and dilated hearts, revealing a relative stenosis of the conus aorticus,[5] than in cases of stenosis of the orifice of the aortic valve. When present, they were found just beneath the narrowed conus. In five cases of this series, these pockets led to the discovery of the stenosis. It might be of interest to mention that in four instances the stenosed conus and systolic pockets were found in cases of syphilitic involvement of the aortic valve with insufficiency of this valve and with typical diastolic pockets. The hypertrophy and dilatation of these hearts, due to aortic regurgitation, had led to the relative stenosis of the conus arteriosus. It was pointed out previously that it is possible that the friction of the systolic blood stream and pressure are sufficient to produce the mechanical irritation of an area situated in the region of the stenosed conus. At the same time, the continuous impulse of the systolic blood stream and pressure might result in the formation of pockets.

Systolic pockets have often been recognized and their significance disputed. Kaewel [6] reported systolic pockets in one case without apparent stenosis of the aortic orifices. Böger [7] denied the presence of valvular disease in one of his cases. In both instances, however, a relative stenosis of the conus aorticus could not be ruled out. Wertkin [8] recently held the systolic blood stream responsible for the formation of systolic pockets in cases of relative or absolute stenosis of the aortic conus. Wolff [9] believed that both the primary circumscribed endocardial thickening and the secondarily formed systolic pocket were the results of the systolic pressure in his case of stenosis of the aortic orifice. Krasso, however, maintained that the primary endocardial thickening which later may be the seat of a systolic pocket is the result of the

5. The conus aorticus, often called conus arteriosus sinister, is the uppermost portion of the left ventricular cavity, just below the aortic valve (Krasso).

6. Kaewel, H.: Beitr. z. path. Anat. u. z. allg. Path. **79**:431, 1928.

7. Böger, A.: Beitr. z. path. Anat. u. z. allg. Path. **81**:441, 1929.

8. Wertkin, I. M.: Virchows Arch. f. path. Anat. **280**:87, 1931.

9. Wolff, K.: Virchows Arch. f. path. Anat. **280**:107, 1931.

regurgitating columns of blood in cases in which there is also an aortic insufficiency. If, in addition to the valvular insufficiency, a stenosis of the aortic conus exists, systolic pockets may be formed secondarily. In other words, systolic endocardial pockets, according to Krasso, signify both stenosis of the aortic conus and insufficiency of the aortic valve. Because of the fact that in a number of my cases and in instances reported in the literature systolic pockets were present without

Fig. 2.—Anatomic studies showing: *a*, systolic pockets, stenosed conus aorticus and perforated septum (probe); *b*, right ventricular aspect of heart shown in *a* (note the perforated septum (probe), thickened medial leaflet of the tricuspid valve and pocket); *c*, perforated fossa ovalis and auricular pocket, the opening of which is directed toward the perforated fossa ovalis; *d*, defect in membranous septum, and *e*, right ventricular aspect of heart shown in *d* (note the septum defect, the thickened medial leaflet of the tricuspid valve and the huge vegetation to the right).

any evidence of aortic insufficiency, it must be emphasized that systolic pockets are pathognomonic of stenosis, either of the aortic orifice or of the conus aorticus.

INSUFFICIENCY OF THE MITRAL VALVE

In the course of this study, circumscribed areas of thickenings in the left auricle were encountered in four instances of healed endocarditis of the mitral valve. In two other cases, endocardial pockets, their openings directed toward the mitral valve, were present in the left auricle. One of these cases was reported elsewhere. In all these instances an underlying primary inflammation could be demonstrated histologically, with the presence of many lymphocytes, endothelial cells and a few polymorphonuclear leukocytes, in addition to much fibrosis. While these findings easily explain the circumscribed areas of thickenings on the basis of a primary inflammation, they fail to explain the formation of pockets. It must be assumed that another causative agent transformed these circumscribed areas of thickening into pockets. Because of the fact that these pockets were open toward the mitral valve, it is likely that whatever had caused their formation must have come from the direction of the mitral valve. The only possible explanation of a force exerting its effect from this direction is that of a regurgitating blood stream and pressure due to insufficiency of the mitral valve. In other words, endocardial pockets in the left auricle with openings directed toward the mitral valve are pathognomonic of insufficiency of the mitral valve.

PHYSIOLOGIC PATENCY OF A SEPTUM DEFECT, FORAMEN OVALE AND PERFORATED FOSSA OVALIS

In the present series two cases were encountered which revealed morphologic evidence of the flow of blood through a patency in the intraventricular septum. The first case revealed an old endocarditis of the aortic valve and a marked hypertrophy and dilatation of the heart. The conus aorticus was narrowed. Within a distance of about 1.5 cm. from the base of the aortic valve, a series of three endocardial pockets was found, their openings directed toward the apex of the heart (systolic pockets). The endocardium between the base of the aortic valve and the endocardial pockets showed many areas of endocardial thickening and a perforation which led from the left into the right ventricle. The diameter of the perforated area in its left ventricular aspect measured 8 mm. and in its right 5 mm. The medial tricuspid leaflet corresponding to the perforation was thickened and showed a hematoma. Just beneath the perforation in the right ventricle there was an endocardial pocket, the opening of which was directed toward the perforation. In the periphery of the pocket several small areas of endocardial thickening could be made out.

The presence of the endocardial pocket in the right ventricle corresponding to the perforated septum is significant. No sections were

taken from this pocket, and therefore it cannot be decided whether or not the primary endocardial thickening which preceded the formation of the pocket in the right ventricle was the result of a healed mural endocarditis. It is equally possible that the force of the blood stream and pressure coming through the perforated septum might have caused the thickening merely by mechanical irritation. The continuous pressure directed on the fibrosed region secondarily had caused the formation of the pocket. The best explanation which can be offered for these pockets, therefore, lies in the assumption that during life, blood must have circulated through the perforated septum. In other words, this pocket is an anatomic witness of the interchange of blood between the ventricles. The presence of the systolic endocardial pockets in the left ventricle may be taken as proof of stenosis either of the aortic orifice or of the conus aorticus. The perforation of the septum was probably the result of an old ulcerating mural endocarditis.

Sternberg [10] described one case which in many respects was similar to this one. He did not believe that the systolic pockets in the left ventricle were the result of a congenital anomaly, but stressed a mechanical genesis. He also emphasized that a mural endocarditis might accentuate the primary endocardial thickening which led to the formation of pockets.

The other case in this series was that of a child about 1 year old. At autopsy, the heart revealed a patent membranous septum. The margin of the opening at its right ventricular aspect was thickened and white. The medial leaflet of the tricuspid valve corresponding to the region of the defect in the septum revealed a circumscribed area of thickening. At the thickened portion of the medial tricuspid leaflet a large gray, soft and friable vegetation was found, which on smears revealed many gram-positive cocci. The remainder of the tricuspid was tender, smooth and glistening. There also was an organizing bronchopneumonia. The blood culture, taken at the time of autopsy, revealed hemolytic streptococci.

The circumscribed thickening of the tricuspid leaflet was the result of the mechanical irritation brought about by the columns of blood and pressure of the blood which circulated through the hole in the septum. When bronchopneumonia developed, and as a result of the bronchopneumonia a bacteremia, the bacteria selected the site of the primary injury of the tricuspid and caused the endocarditis. In other words, both the thickened portion of the tricuspid and the final acute vegetative (bacterial) endocarditis of the tricuspid make it evident that during life blood must have circulated through the patent membranous septum. It may be of interest to mention that Sternberg also described three cases

10. Sternberg, C.: Verhandl. d. deutsch. path. Gesellsch. **25**:238, 1930.

of defect in the septum with circumscribed thickenings of the subvalvular region of the right ventricle. Two of his cases also revealed circumscribed thickenings of the tricuspid valve corresponding to the patency in the septum.

The next two instances reveal evidence of circulation of blood through a perforated fossa ovalis and a patent foramen ovale, respectively. The first heart revealed an acute verrucous and ulcerating endocarditis of the mitral valve, superimposed on a healed endocarditis. In the region of the fossa ovalis there was a round opening measuring about 8 mm. in diameter, the wall of which was thickened, firm and slightly ragged. This opening had established a communication between the left and the right auricles. Between this opening and the posterior leaflet of the mitral valve there was one large somewhat horse-shoe-shaped pocket with two smaller ones, the openings of all of which were directed toward the perforated fossa ovalis. Because of the size and form of the perforation and because of the presence of inflammatory cells, it is more likely that the perforation was the result of a mural ulcerating endocarditis in the region of the fossa ovalis than a primary patent foramen ovale.

The auricular pockets are significant because they point toward a flow of blood through the perforated fossa ovalis. The sections of the pockets revealed simple fibrosis and hyalinization but hardly any inflammatory cells or blood pigment. Therefore, it is likely that the pockets were caused by simple mechanical irritation brought about by the columns of blood and pressure of the blood circulating through the perforated fossa ovalis. This irritation first produced circumscribed endocardial thickenings and secondarily the pockets. The pockets also indicate that blood must have circulated from the right into the left auricle.

The second case of this group revealed an old and a recent verrucous endocarditis of the mitral valve. The myocardium showed many Aschoff nodules. There was a patent foramen ovale. The free margin of the foramen in one aspect was studded with small gray verrucae similar to those on the mitral valve. They were found only on the right auricular surface of the free margin of the foramen ovale. It might be emphasized especially that verrucae were present in these two locations only. The acute verrucous endocarditis of the free margin of the foramen ovale is significant from several points of view. First, the presence of verrucae confined to the free margin of the foramen ovale may be taken as evidence that the foramen ovale was patent during life and that blood passed through it. Second, the conclusion may be drawn that blood circulated from the right into the left auricle because of the fact that only the right auricular portion of the foramen ovale showed the verrucae. This corresponds to the finding of verrucae at

the line of closure at the auricular aspect of the mitral valve. Third, these findings may indicate that whatever had caused the appearance of the verrucae was brought to the margin of the foramen ovale through the circulating blood rather than through endocardial vessels, because otherwise their presence confined to this particular location cannot be explained. If this is true, it is much more likely that a verrucous valvular endocarditis also is the result of an injury brought to the valve by the

Fig. 3.—Anatomic study showing the verrucae at the margin of the formen ovale.

passing circulating blood rather than by means of intravalvular blood vessels. As far as the scope of this paper is concerned, it must be emphasized that a verrucous endocarditis of the free margin of the foramen ovale is evidence of blood circulating from the right to the left auricle.

DILATATION OF THE HEART

This diagnosis can often be made from the gross observation of flattened papillary muscles and trabeculae carneae or of flattening of the inner walls of the cardiac chambers. According to statements in

the literature (Dehio,[11] Mönckeberg[12]), hyperplasia of the interstitial connective tissue of the heart (myofibrosis cordis) is characteristic of dilatation of the heart. Hyperplasia of the interstitial connective tissue was a common finding in the dilated hearts used for this study. Sometimes, however, difficulties arose in distinguishing myofibrosis cordis from connective tissue proliferation from other causes.

In a previous study in collaboration with Karsner,[13] it was noted that segmentation of the muscle fibers was especially frequently encountered in hypertrophic hearts. It was observed at that time that the intercalated disks became distinctly visible in dilated hearts. The conspicuous appearance of the intercalated disks was called "readiness toward separation of the heart muscle fibers." In this study, therefore, special attention was directed toward the appearance of the intercalated disks. While in the nondilated hearts the intercalated disks were hardly noticeable, by the use of the hematoxylin-eosin stain they were prominent and easily demonstrable in the dilated hearts. They were more pronounced in the muscle fibers situated close to the endocardium than in those close to the epicardium. Since particular attention has been paid to the intercalated disks, it is possible to confirm a histologic diagnosis of dilatation of the heart by the autopsy records of flattened papillary muscles and columnae carneae. Whether the prominence of the intercalated disks alone offers sufficient ground to warrant a diagnosis of dilatation of the heart is at present difficult to decide, since so little is known of the purpose and function of the disks. However, from this study it appears that the conspicuous appearance of the intercalated disks in a large number of hearts is often characteristic of dilatation of the chambers.

SUMMARY

Endocardial pockets of the left ventricle which are open toward the aortic valve are pathognomonic of insufficiency of the aortic valve. Endocardial pockets in the left ventricle which are open toward the apex of the heart are pathognomonic of stenosis either of the orifice of the aortic valve or of the conus aorticus. Pockets in the left auricle with their openings directed toward the mitral valve are characteristic of insufficiency of this valve. Left auricular or right ventricular pockets with their openings directed toward a perforated auricular or ventricular septum, respectively, are indicative of an *intra vitam* circulation of blood through the perforated region in the direction of the openings

11. Dehio, K.: Deutsches Arch. f. klin. Med. **62**:1, 1898.

12. Mönckeberg, J. G.: Die Erkrankungen des Myokards und des spezifischen Muskelsystems, in Henke, F., and Lubarsch, O.: Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, Julius Springer, 1924, vol. 2, p. 290.

13. Saphir, O., and Karsner, H. T.: J. M. Research **44**:539, 1924.

of the pockets. A circumscribed endocarditis of the tricuspid valve in an area corresponding to a defect in the interventricular septum indicates a flow of blood from the left to the right ventricle through the patency in the septum. A recent verrucous endocarditis at the right auricular aspect of the margin of a foramen ovale signifies a flow of blood through the foramen from the right to the left auricle. Two cases illustrating these conditions are reported. Prominent intercalated disks favor the diagnosis of a dilatation of the heart.

LYCOPODIUM GRANULOMA

ITS CLINICAL AND PATHOLOGIC SIGNIFICANCE, TOGETHER WITH A NOTE ON GRANULOMA PRODUCED BY TALC

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The inflammatory reactions produced experimentally by means of the spores of Lycopodium have been extensively studied for many years and are well known. That these spores may be of importance in the production of lesions in man simulating tuberculous or neoplastic disease is not generally appreciated and needs to be emphasized. The problem was brought to my attention by a series of puzzling cases in which persistent sinuses, masses or tubercle-like lesions developed at the sites of previous operations. The nature of these lesions was at first not clear. However, microscopic examination of the surgical specimens revealed the common etiologic factor to be the spores of Lycopodium. Investigations showed that Lycopodium had probably been introduced into the wounds at the time of previous operations in a dusting powder of which it is an ingredient. Inquiry established the fact that powders containing spores of Lycopodium are used in the operating rooms of hospitals in the preparation of gloves and other rubber supplies.

REPORTS OF CASES

CASE 1.—A Spaniard, aged 35, was admitted to the hospital because of a persistent sinus and a mass in the epididymis. A history was obtained of an operation for traumatic hydrocele two months previously. A clinical diagnosis of tuberculous epididymitis was made, and an orchidectomy was performed. In the surgical specimen, the epididymis was found to be replaced by a firm, pearly white tissue, in the meshes of which were cellular and necrotic areas. Microscopic examination revealed the cellular areas to be composed of a type of granulation tissue containing numerous plasma cells, lymphocytes and giant cells of both the foreign body and the Langhans variety (fig. 1 *A*). Polymorphonuclear leukocytes were abundant in the more superficial layers. Within the granulation tissue, as well as within the giant cells proper (fig. 1 *B*), spores of Lycopodium as described later were found.

CASE 2.—During the course of a nephrectomy for pyelonephritis, in an 8 year old boy, a persistent renal sinus tract was encountered and resected. The history revealed that the condition had developed two months after the drainage and subsequent removal of a perinephric hematoma. Examination of the sinus tract showed a histologic picture similar to that in case 1. Spores of Lycopodium were also found within the sinus tract.

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CASE 3.—A man, aged 54, gave a history of the removal of stones from the urinary bladder eight years previously, with periodic irrigations since that time. Another stone had been removed from the bladder six weeks previously. On admission to the hospital, a fleshy polypoid bar of prostatic tissue causing obstruction at the vesical neck was seen by cystoscopy. This was diagnosed as a carcinoma, and three small specimens were removed by means of a prostatic punch. On microscopic examination, the tissue was seen to contain areas of round cells and of plasma cells interspersed with nodules the size of a millet seed composed of epithelioid cells, giant cells and vacuolated cells, the latter being probably of histiocytic origin. Occasional small necrotic areas were found in the center of these accumulations. Spores of Lycopodium identical with those described later were seen within the nodules as well as within the giant cells. Because of the superficial resemblance of the lesion to tuberculosis, a section was stained by the Ziehl-Neelsen method. The spores were found to be acid-fast; no tubercle bacilli were found.

CASE 4.—A woman, aged 37, with a history of a cholecystectomy performed three months previously, entered the hospital complaining of pain in the epigas-

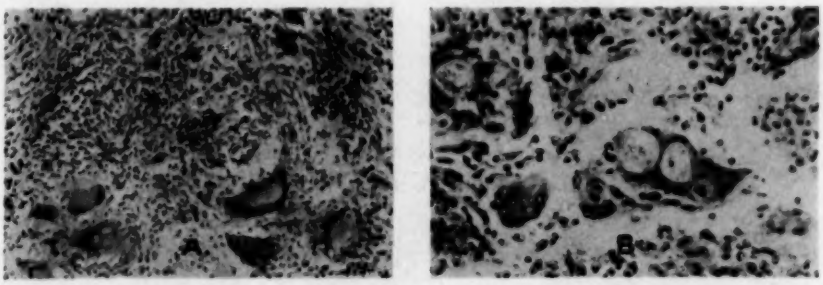

Fig. 1 (case 1).—*A*, the type of reaction; *B*, spores of Lycopodium within giant cells.

trium, distention and vomiting. At exploratory laparotomy numerous adhesions were seen, mainly in the right upper quadrant. The visceral and parietal peritoneum were studded by numerous pearly gray nodules, 1 mm. in diameter, many of which were coalescent. These nodules resembled tubercles so much that a diagnosis of tuberculosis of the peritoneum was made. Biopsy showed the lesion to be composed of nodules within which were areas of necrosis surrounded by epithelioid cells, round cells and giant cells of the Langhans type (fig. 2 *A*). The lesion was at first thought to be tuberculous. However, the Ziehl-Neelsen stain was negative for tubercle bacilli, but it revealed one or two acid-fast spores of Lycopodium in each of the tubercle-like structures (fig. 2 *B*). A very occasional spore was found within a giant cell. The spores, which stain faintly with eosin, were not visualized in the first routine sections, because they were situated within the necrotic zones. This case illustrated the similarity of these granulomatous nodules to tubercles not only on gross inspection but also on routine microscopic examination with ordinary stains. A similar case has been described by Roth.[1] In that instance, also, a diagnosis of tuberculosis of the peritoneum was made at the time of operation.

1. Roth, H.: Frankfurt. Ztschr. f. Path. **29**:59, 1923.

CASE 5.—A Negro with a history of incision and drainage for suppurative adenitis of the neck three months previously, entered the hospital because of a persistent sinus at the site of incision. At operation the sinus tract and adjacent lymph nodes were removed. Microscopic examination of the sinus tract showed a chronic inflammatory process. There were spores of Lycopodium among the lymphocytes and also within the giant cells. The lymph nodes showed typical tuberculous adenitis. Ziehl-Neelsen stain demonstrated acid-fast bacilli in the lymph nodes, and spores of Lycopodium in the sinus tract. There were also

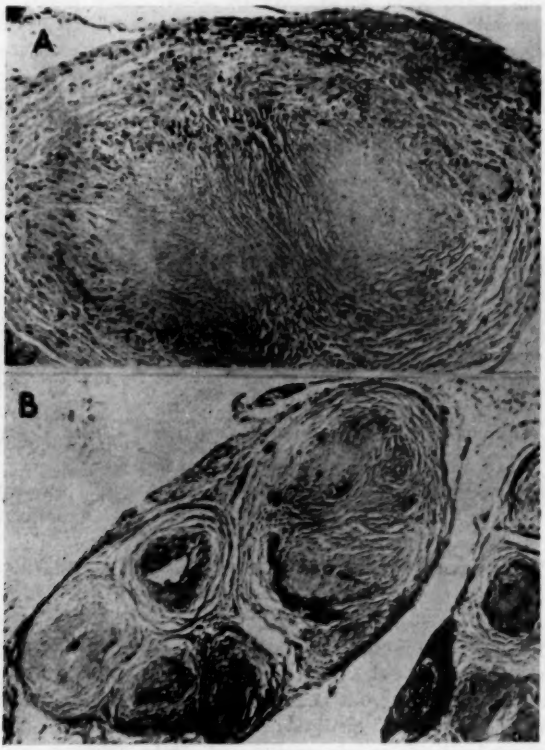

Fig. 2 (case 4).—*A*, tubercle-like nodules of peritoneum; hematoxylin and eosin stain. *B*, same as *A*, showing acid-fast spores of Lycopodium within nodules; Ziehl-Neelsen stain.

crystals of talc in some of the giant cells within the wall of the sinus tract. This case was therefore considered to be one of tuberculous lymphadenitis, complicated by granuloma due to Lycopodium and to talc. In this case the spores of Lycopodium were most likely only an incidental finding and played no part in the clinical picture. An instance of this nature is represented by the case of de Messer,[2] who found spores of Lycopodium in a squamous cell carcinoma of the forearm in which the Lycopodium probably gained entrance through the skin.

2. de Messer, A. F.: Virchows Arch. f. path. Anat. **163**:111, 1901.

CASE 6.—A man, aged 30, who had had an adenoma of the breast removed, entered the hospital seventeen months later, complaining of numerous tender nodules in the region of the incision. A tentative diagnosis of carcinoma was made. The slides from the original tumor were examined, and no evidence of a malignant condition was found. This patient, however, had had his original operation at a hospital where a dusting powder containing Lycopodium was used, so that the possibility of granuloma due to Lycopodium was suggested. On removal and examination of the scar, this opinion was confirmed. A picture similar to that in case 3 was found, the spores being contained within the tubercle-like nodules. No tubercle bacilli were found.

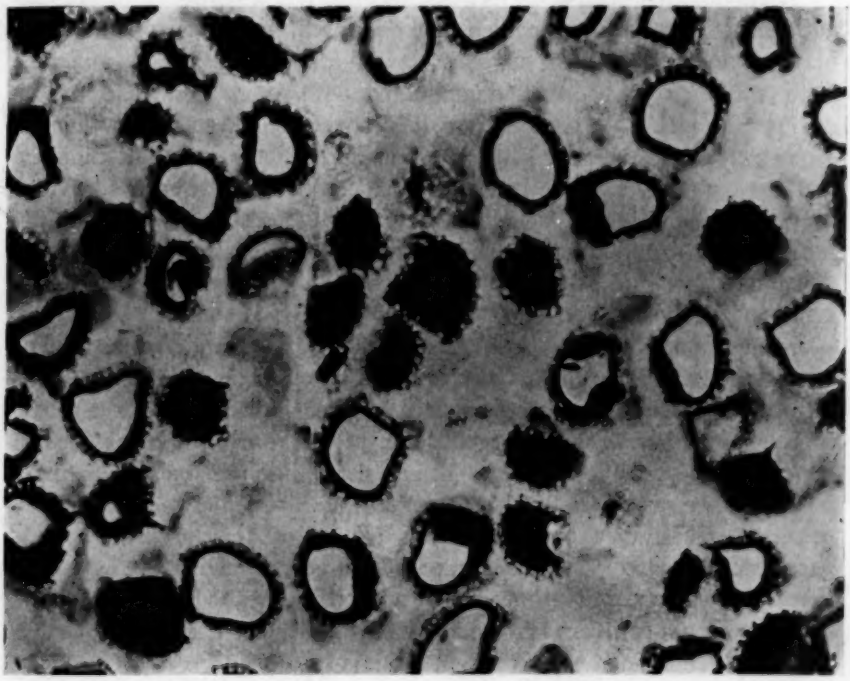

Fig. 3.—Spores of Lycopodium in section.

PATHOLOGY OF THE LESION

The lesion is essentially granulomatous, a reaction to the spores of Lycopodium. It is composed of granulation tissue, usually in the form of nodules, and contains epithelioid cells and giant cells of the foreign body as well as the Langhans type. There are usually extensive areas of fibrosis and some areas of necrosis. The spores may be seen within the granulation tissue and also within the giant cells themselves. When stained by the ordinary methods they are poorly visualized. However, the Ziehl-Neelsen stain reveals them as acid-fast, bright red, circular bodies, averaging 30 microns in diameter. The contour is scalloped,

and the edges have short spinous processes. Some of the spores are hollow, while others are filled with coarsely granular material. Some show an opening formed by three sides which are also covered with spinous processes. Reconstruction in three dimensions reveals the spores to be irregularly spheroidal bodies of a nodular mulberry appearance, covered with spinous projections (fig. 3). No change is noted in their morphology after treatment with weak acids or bases.

COMMENT

Lycopodium, because of its fine spicules, has a tendency to become adherent to any tissue on which it is deposited, and on manipulation it may be forced beneath the surface. It is therefore possible for an operative specimen to become contaminated with spores of Lycopodium during removal. To demonstrate this, the freshly removed specimen from a patient operated on for acute appendicitis was intentionally handled with gloves which had been powdered with these spores. After the specimen had been dehydrated, embedded, sectioned and stained, microscopic examination revealed many of the spores completely embedded within the tissue. It is obvious that this may lead to an error in diagnosis. To avoid such an error it is necessary that the spores be found within giant cells or within a granulomatous lesion. This was the case in all of the instances recorded here.

Animal inoculation with the spores of Lycopodium clavatum resulted in the formation of granulation tissue after from two to six weeks, which on microscopic examination was not unlike the reaction in man, including the presence of the spores within the giant cells. Further experimental studies on the various phases of this problem are in progress. No attempt will be made in this paper to review the extensive literature on experimental lesions produced by Lycopodium.

It is also possible that the crystals of magnesium silicate (talc) produce such lesions. This idea obtains support in the finding of the crystals within the giant cells in the fistulous tract in case 5.

The following case demonstrates the formation of minute talc granulomas in an otherwise normal appendix.

CASE 7.—A man, aged 34, had had an operation for volvulus of the sigmoid eight years previously, and one for separation of adhesions with resection of the sigmoid eight months previously. During the present hospitalization, an appendectomy was performed and an apparently normal appendix removed. On microscopic section, granulomas were observed in the serosa; and within giant cells there were present refractile bodies morphologically identical with the crystals of talc.

SUMMARY

Granulomatous lesions grossly resembling tuberculosis or neoplasm and resulting in the formation of persistent sinuses may be produced

by the surgical use of dusting powders containing as an ingredient spores of Lycopodium.

Macroscopically and microscopically, the lesions may be confused with those of tuberculosis; however, the Ziehl-Neelsen stain shows the presence of the acid-fast spores of Lycopodium.

The spores can be considered the causative agents of such lesions only when found within giant cells or within granulomatous nodules.

These spores should not be used as an ingredient of dusting powders which come in contact with open wounds.

Similar granulomatous lesions may also be caused by talc.

LEIOMYOMA OF THE PROSTATE

REPORT OF THREE CASES

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Overgrowth of the epithelial components of the prostate is usually accompanied by overgrowth of the fibromuscular stroma. However, neoplastic proliferation of the stroma alone is rare. A review of the available literature yielded records of only eight cases of leiomyoma of the prostate. During the past year, solitary myomatous nodules were observed in three of the prostates received in the Laboratory of Surgical Pathology of the New Haven Hospital. A report of these cases with a brief review of those previously described is presented here.

REPORT OF CASES

CASE 1.—A 59 year old man was admitted to the New Haven Hospital (Dr. Deming's service) on July 20, 1932, complaining of frequency, burning and pain on urination of three or four years' duration. He stated that during part of this time he was treated for cystitis, and that beginning about one month before admission there developed a sense of fulness above the pubis, hesitancy, dribbling, occasional incontinence and inability to empty the bladder completely. No history of venereal disease was obtained.

On admission he appeared to be in fairly good condition. The systolic blood pressure was 188 mm. of mercury, and the diastolic 100 mm. The external genitalia showed nothing unusual except a small left hydrocele. On rectal palpation the prostate was not tender, and it appeared moderately firm and symmetrically enlarged to about two and a half times its usual size. The median groove and furrow were absent. With a catheter 1,000 cc. of urine was obtained and immediately replaced by sterile physiologic solution of sodium chloride. The urine contained a few white blood cells, and no albumin or sugar. The bladder was then slowly decompressed by an inlying catheter. The phenolsulphonphthalein excretion was 45 per cent in two hours. The nonprotein nitrogen of the blood was 118 mg. per hundred cubic centimeters. Five days later (July 25) it was 43 mg. Cystoscopic examination on August 2 revealed a solitary large calculus in the bladder, several small diverticula in the fundus of the bladder and enlargement of both lateral lobes and the median lobe of the prostate. The following day the calculus was removed through a suprapubic cystostomy, and a bilateral vasotomy was performed. The calculus measured 2 cm. in diameter and had the shape of a jackstone. Following the operation the patient continued to have an elevation of temperature to between 100 and 101 F. On September 1, signs of

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pneumonia developed in the right lung, accompanied by a further rise in temperature to between 102 and 103 F. During the next two weeks he received several blood transfusions, and his condition improved so that after September 16 he was out of bed most of the time. On September 28, a suprapubic prostatectomy was performed by Dr. P. W. Skinner. Following the operation the patient's condition steadily improved, and he was discharged on October 25 in good condition.

Description of Specimen.—Of the five pieces of firm gray tissue, varying in size from 2 by 1 by 0.5 to 4 by 3 by 1.5 cm., one was roughly globular and firmer than the rest. It measured 2 cm. in diameter, and on cut section had a whorled appearance of interlacing bundles and a watered-silk luster. While no glandular

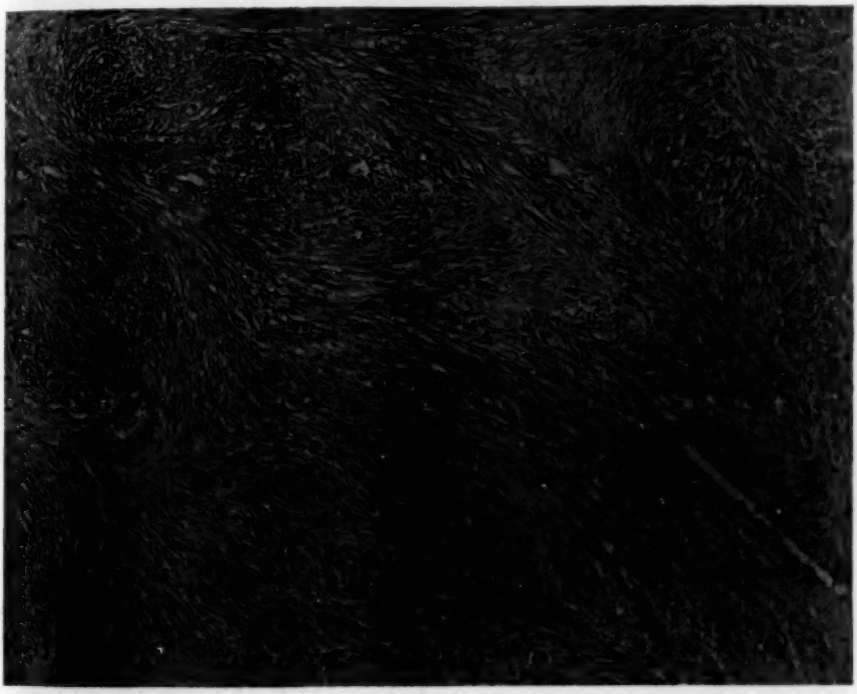

Fig. 1.—Leiomyoma of the prostate in a 65 year old man (case 2). The interlacing arrangement of the smooth muscle bundles is shown; × 100.

tissue could be made out grossly in this nodule, this was quite evident in the other pieces. In microscopic preparations the nodule was surrounded by a fibrous connective tissue capsule and was composed of interlacing smooth muscle bundles and no glandular elements. In sections stained by the methods of Mallory (aniline blue) and of van Gieson, a delicate network of fine connective tissue fibrils was seen between the muscle bundles. The other pieces of tissue showed glandular overgrowth and an increase of the fibromuscular stroma.

Case 2.—A 65 year old night watchman was admitted to the New Haven Hospital (Dr. Deming's service) on Aug. 9, 1932, complaining of hesitancy, frequency, dribbling and burning on urination and occasional incontinence. His symptoms had begun thirty years before, but had increased in severity during the

last two years. He was now voiding hourly and complained of inability to empty the bladder completely. No history of venereal disease was obtained.

On admission he was semistuporous. The systolic blood pressure was 140 mm. of mercury and the diastolic 70 mm.; the pulse rate was 84 per minute and the temperature 99.5 F. The external genitalia appeared normal except for bilateral, easily reducible inguinal hernias. On rectal palpation the prostate was not tender, was of rubbery firmness and was symmetrically enlarged to a moderate degree.

The day following admission signs of bronchopneumonia developed, but the patient recovered. On August 19, the phenolsulphonphthalein excretion was from 55 to 60 per cent in two hours. The nonprotein nitrogen of the blood was 47 mg. per hundred cubic centimeters. Ten days later it was 31 mg. per hundred cubic centimeters. Cystoscopic examination on that day (August 29) revealed numerous small diverticula in the bladder and a diffuse enlargement of the prostate. On August 30, a perineal prostatectomy and bilateral vasotomy were performed by Dr. P. W. Skinner. Following the operation the wound healed slowly. On September 28, a recto-urethral fistula developed which healed spontaneously in about two weeks. The perineal wound was still draining slightly when the patient was discharged on November 17, but ceased draining by December 6.

Description of Specimen.—A smooth rounded nodule was attached to one of the six pieces of prostatic tissue varying in size from 1.5 by 1 by 1 to 3 by 2 by 1 cm. The nodule measured 12 mm. in diameter, was firmer than the rest of the tissue, and had a uniform grayish-white whorled appearance on the cut surfaces. The other pieces had a glandular structure. In microscopic preparations the nodule was composed of interlacing smooth muscle bundles in an abundant fibrous connective tissue stroma (fig. 1). This structure was clearly brought out in preparations stained by the method of van Gieson. The nodule of smooth muscle tissue was sharply demarcated from the surrounding glandular tissue, although no definite connective tissue capsule could be made out. Preparations from the other pieces showed enlarged prostatic acini embedded in an abundant fibromuscular stroma. Some of the lumens of the acini were lined by columnar cells; others appeared distended and lined by low cuboidal epithelium. An infiltration with small round cells was noted in some areas of the stroma.

CASE 3.—A 67 year old man was seen by Dr. Alfred C. Carpenter of Milford, Conn., early in 1932. At this time the patient complained of urinary difficulty of about four years' duration, consisting of marked straining in starting the urinary stream and of some dribbling after urination. No history of venereal disease was obtained.

On rectal palpation the prostate was slightly enlarged, hard and not tender. A catheter (no. 20 French) was passed without difficulty. No residual urine was obtained. Subsequently urination gradually became more difficult. When seen in February, 1933, the patient stated that for the previous six months he had to void hourly and was unable to empty the bladder completely. Dribbling also increased. He complained of no pain at any time and appeared to be in good general health. At this time further enlargement of the prostate, in the middle lobe only, was noted on rectal palpation. The residual urine amounted to about 250 cc. On February 24, a suprapubic cystostomy, and on March 12, a prostatectomy, were performed by Dr. Carpenter. The patient made a good recovery. All wounds were healed when the patient was discharged on April 11.

Description of Specimen.—The specimen consisted of a roughly Y-shaped mass of prostatic tissue, measuring approximately 5 by 5 by 2 cm. The arms of the Y represented portions of the lateral lobes and the base of the Y, the enlarged

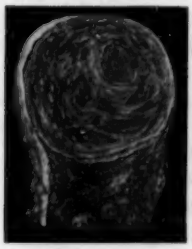

Fig. 2.—Drawing of a sagittal section through the prostate of a 67 year old man (case 3). The round encapsulated leiomyomatous nodule has a characteristic whorled appearance.

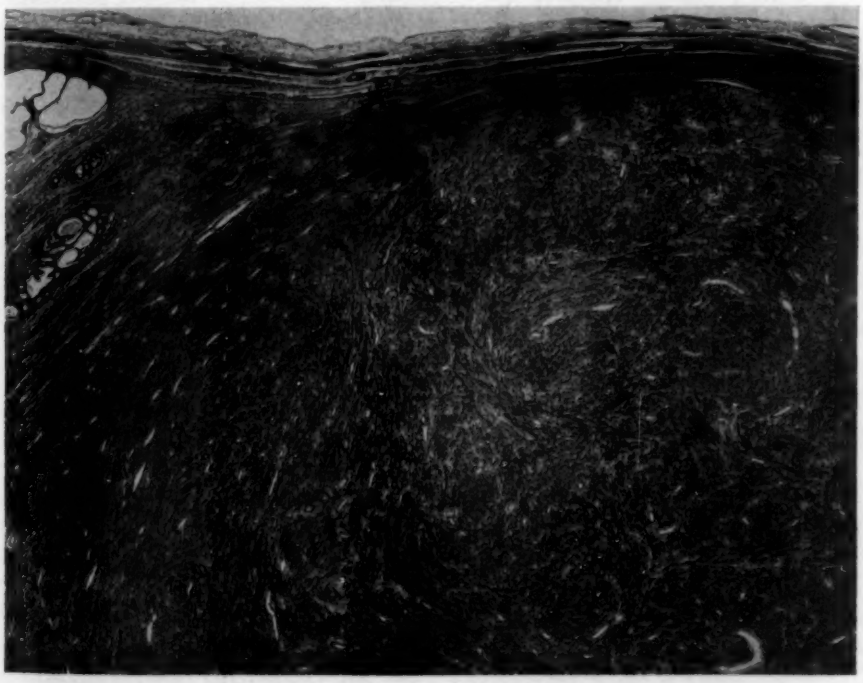

Fig. 3.—Leiomyoma of the prostate (case 3). The interlacing smooth muscle bundles forming the tumor are surrounded by a definite fibrous connective tissue capsule; × 12.

median lobe. The enlargement of the median lobe was symmetrical and spherical. This portion was firmer than the lateral lobes. A sagittal section of the specimen (fig. 2) revealed a circumscribed, round, encapsulated mass of firm tissue, 2 cm. in diameter, with a whorled appearance and a grayish-white, watered-silk luster. No glandular tissue could be seen within this nodule. Sections through the lateral lobes showed masses of glandular tissue. In microscopic preparations the nodule in the median lobe was seen to be composed of interlacing bundles of smooth muscle in a delicate fibrous connective tissue stroma. This was particularly well seen in preparations stained by the method of van Gieson. The nodule was surrounded by a well developed and complete fibrous connective tissue capsule (fig. 3). Endothelial lined vascular channels were numerous throughout. No glandular elements were present. The adjacent tissue and the lateral lobes were composed of small masses of glandular tissue embedded in a dense fibromuscular stroma. The glands varied considerably in size and shape. Their lining epithelium was tall columnar, and there were numerous papillary infoldings of the mucosa. In others the lumens were distended and the lining epithelium flat.

CASE REPORTS FROM THE LITERATURE

LEBEC'S [1] CASE.—The first case of leiomyoma of the prostate was presented before the Société Anatomique in Paris at its meeting on Feb. 18, 1876, by Lebec. The patient was a 76 year old man, admitted to the Hôtel Dieu (Guérin's service) on Jan. 5, 1876, with urinary retention. He complained of no pain except that caused by distention of the bladder. Difficulty was encountered in introducing a metal sound, but a soft rubber catheter passed easily, and 1.5 liters of clear urine was obtained. After this the patient was catheterized three times daily, and pus soon appeared in the urine. The patient died of pneumonia on January 15. At necropsy, the urinary bladder was enlarged and trabeculated, and it contained two small calculi. The prostate measured 5.5 cm. transversely and 6 cm. longitudinally, and the length of the distorted prostatic portion of the urethra was 10.5 cm. Superimposed on the median lobe there was a circumscribed tumor nodule which shelled out easily. Microscopic examination showed it to be composed of smooth muscle fibers resembling those of the uterus.

DAMSKI'S [2] CASE.—The second case of leiomyoma of the prostate was reported by Damski, from Russia, in 1924. The patient, a 62 year old farmer, complained of a visible swelling in the perineal region, causing marked difficulty and pain on defecation. He had no urinary symptoms. In the perineum a little to the right of the midline, near the anus, there was a walnut-sized swelling. On rectal palpation a voluminous, smooth, spherical and not tender tumor was felt at the site of the prostate. The upper margin of this could not be reached. On cystoscopic examination there was no residual urine; the bladder appeared normal except for some reddening and edema of the trigone. Examination of the urine gave negative results. The tumor was removed piecemeal by a perineal approach. The patient, when discharged eighteen days later, was free from symptoms. The removed pieces of tissue were grayish white and weighed 180 Gm. Microscopic preparations from many parts of the tumor showed it to be composed entirely of smooth muscle tissue.

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1. Lebec: Progrès méd. **4**:471, 1876.
2. Damski, A.: Ztschr. f. urol. Chir. **16**:47, 1924.

BUGBEE'S [3] CASE.—Bugbee, in 1926, reported a leiomyoma of the prostate in a 49 year old man, who was admitted to the St. Luke's Hospital in New York on May 24, 1925, with complete retention of urine. The patient's urinary symptoms commenced about two weeks previous to admission, when he began to have a poor stream and a tendency to dribble. On the day before admission he was unable to void and was catheterized. On rectal palpation the prostate appeared symmetrically enlarged. The right lobe felt softer than the left, and there was slight induration over the left lobe. A catheter was introduced and left in place for the next seven days, during which the patient's temperature ranged between 99 and 101 F. At this time tenderness, softening and fluctuation were felt over the left lobe on rectal palpation. With the object of draining the abscess an external urethrotomy was performed. A mass of soft friable material extending well beyond the reach of the finger filled the space between the bladder and rectum. About 12 ounces (340 Gm.) of this material was removed. Microscopic examination of the fragments showed them to be composed of smooth muscle tissue. The patient lost 30 pounds (13.6 Kg.) in weight. He received roentgen therapy over a period of four months. Since then his condition had slightly improved. The perineal wound opened several times, with a temporary leakage of urine. The suprapubic drainage was maintained.

RUBRITIUS' [4] CASE.—Rubritius, in 1927, reported the case of a 70 year old man who for some time had had incomplete retention of urine. The residual urine amounted to 400 cc. The prostate was "the size of a tangerine," moderately firm and smooth. Through a suprapubic cystotomy, a mass about the thickness of two thumbs protruded 8 cm. into the bladder, encircling about three fourths of the urethral orifice. The mass shelled out easily and consisted of several nodules. On microscopic examination it was seen to be composed of interlacing bundles of smooth muscle. At the periphery of a nodule glandular prostatic tissue was present in a few places.

WOLMAN'S [5] CASE.—Wolman, in 1931, reported the case of a 73 year old merchant, who entered the Pennsylvania Hospital on Aug. 31, 1929, complaining of urinary retention, frequency, which was more marked at night, pain in the region of the bladder and loss of weight. These symptoms had increased in severity since their onset fourteen months previously. On examination a large intra-abdominal tumor was discovered and enlargement of the prostate noted. An indwelling catheter was inserted and allowed to remain. The patient became progressively weaker and emaciated and died of cachexia and terminal lobular pneumonia on October 29. At necropsy, a "histioid tumor" arising in the left kidney and metastasizing to the mesentery, retroperitoneum, spinal column and liver was found. The bladder was contracted and had thick trabeculated walls. A rounded firm nodule projected into the bladder. On section this nodule was encapsulated, glistening and pearly white, with whorls of fine fibers. Microscopic preparations showed it to be composed of smooth muscle cells with scanty connective tissue stroma. The tumor was surrounded by prostatic tissue except at its superior pole, where it lay directly beneath the bladder mucosa. No glandular elements were seen in the tumor.

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3. Bugbee, H. G.: J. Urol. **16**:67, 1926.
4. Rubritius: Ztschr. f. urol. Chir. **24**:418, 1928.
5. Wolman, Irving J.: J. Urol. **25**:93, 1931.

HINMAN and SULLIVAN'S [6] CASES.—Hinman and Sullivan, in 1931, reported two cases of leiomyoma of the prostate. The first patient, a 36 year old man, complained of sharp pain in the rectum with a desire for defecation, occasional aching discomfort in the perineum, slight burning on urination and some nocturia. These symptoms had been present for about one year. One year prior to the onset of these symptoms he was told by a physician that the median lobe of the prostate was enlarged. He also had a gonorrheal infection for ten years with recurrent discharge and urethral stricture. On rectal palpation a smooth, rounded, elastic mass was felt. The prostatic furrow and notch were obliterated by the mass. The tumor, removed by a perineal approach, was attached by a narrow pedicle to the prostate near its apex. The underlying prostatic surface was smooth and apparently intact. The tumor mass, when removed, measured 2.5 by 3.5 by 4.5 cm., and had a thin fibrous capsule. On the cut surfaces it exposed interlacing fibromuscular strands. Microscopic preparations showed the tumor to be composed of interlacing strands of smooth muscle through which ran rather large vascular channels. No epithelial elements were noted.

The second patient was a 39 year old man who was admitted to the United States Naval Hospital, Mare Island, on Jan. 13, 1931, complaining of extreme constipation, burning and tenderness in the rectum, aggravated by defecation. The symptoms had begun six months previously, and had increased steadily in severity. His only urinary complaint was nocturia for several years. On rectal palpation a firm, elastic tumor mass, about the size of a baseball, was felt over the prostatic area. The normal markings of the prostate were obliterated. About two thirds of the tumor had been removed by a perineal approach when the patient went into shock. He died the next day. The portion of the tumor removed measured 2 by 2 by 3 cm., and weighed 5 Gm. and was firm and elastic. The cut surfaces exhibited a whorl formation suggestive of a leiomyomatous growth. Microscopic preparations showed irregular bundles of smooth muscle cells supported by fibrous connective tissue.

DEUTICKE'S [7] CASE.—The most recent report of a case of leiomyoma of the prostate came from Vienna and was made by Deuticke, in 1932. The patient was a 65 year old head-forester, who complained of difficulty in passing stools for the previous two months. In spite of a strong desire for defecation he had no stools for days at a time, and only by taking strong cathartics and by hard and exhausting bearing down could he pass any. He complained of no urinary difficulty. On rectal palpation a large, firm, hardly movable, globular tumor with a lobular surface compressed the rectum just above the sphincter. The tumor occupied the prostatic region and did not involve the rectal wall. Cystoscopic examination revealed a few cubic centimeters of residual urine, slight trabeculation of the bladder, elongation of the prostatic portion of the urethra and marked enlargement of the prostate, particularly on the right. The nonprotein nitrogen of the blood was 37.8 mg. per hundred cubic centimeters. The tumor, which was "the size of a man's fist," was shelled out in globular masses by a perineal approach. On microscopic examination all these grayish-white masses proved to be composed of smooth muscle tissue. In preparations stained by the method of van Gieson scanty connective tissue was seen between the interlacing muscle bundles. No epithelial elements were noted. The patient had no symptoms when discharged three weeks following admission.

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6. Hinman, Frank, and Sullivan, J. J.: J. Urol. **26**:475, 1931.
7. Deuticke, Paul: Deutsche Ztschr. f. Chir. **236**:475, 1932

COMMENT

Only eleven cases of leiomyomas of the prostate are available for analysis. Depending on size, location and concomitant changes in the prostate, they produced disturbances either of urination or of defecation. Seven of the patients (those of Lebec, Bugbee, Wolman, Rubritius and us) had urinary symptoms only. The remaining four (patients of Damski, Hinman and Sullivan and Deuticke) had primarily rectal manifestations.

In most of the patients with urinary symptoms the presence of the myomatous nodule perhaps only exaggerated the disturbances due to enlargement of the rest of the prostate. In none of these could the urinary difficulties be attributed to the myomatous growth alone, although the growth arising in the prostate proper (mostly in the median portion) contributed to the distortion of the urethra.

In the group of patients with rectal disturbances, the tumor obviously produced obstruction. Arising in the posterior portion of the prostate, it grew toward the rectum.

The location of these leiomyomas with respect to the prostate and the surrounding organs suggests a genetic difference in the tumor anlage. However, the information thus far available is insufficient to ascertain the validity of this suggestion.

HYPERTENSION WITH RETROPERITONEAL GANGLIONEUROMA AND SOFTENING IN BRAIN AND SPINAL CORD

REPORT OF A CASE IN A YOUNG MAN

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The region of the suprarenal glands is a common site for the occurrence of a group of neurogenic tumors classified as sympathogoniomas, ganglioneuromas and paragangliomas. These tumors have the same embryologic origin as the suprarenal medulla and the adjacent sympathetic ganglions, namely, the primitive sympathogonia which wander into this region. Divergence in the process of differentiation leads to variation in structure and in function.

The most primitive type of tumor in this group is the sympathogonioma (neurocytoma). It is composed of small round cells, about the size of a small lymphocyte, each containing a deeply staining, round, compact nucleus and a scanty amount of cytoplasm. The paraganglioma (pheochromocytoma) is a more mature type of tumor composed of chromaffin cells resembling those of the suprarenal medulla. These large cells are polyhedral. In sections fixed in Zenker's solution the cytoplasm contains characteristic brown granules. The nuclei are large, stain poorly, are very granular and contain one or two nucleoli. The ganglioneuroma is a still more mature neoplastic representative of the primitive stem cell in its divergence and maturation in the direction of the spinal ganglion type of cell.

Paragangliomas have been found in cases of hypertension, and an etiologic rôle in its development has been suggested.

The case reported here is that of a young man who had a high blood pressure in the presence of a ganglioneuroma in the vicinity of the left suprarenal gland.

REPORT OF CASE

On May 2, 1932, a white man, aged 23, entered Passavant Memorial Hospital in the service of Dr. M. H. Barker. He complained of paralysis of the right side of the body, inability to urinate, intermittent pain in the left arm, blindness in the left eye and ringing in the ears.

The illness began six weeks previous to admittance, with pain in the right shoulder and numbness in the forearm and hand. Within a short period of time the arm became paralyzed. Two weeks later pain and numbness were noticed in the left leg. The muscles of speech were also affected. On April 26, the patient

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suddenly became unable to urinate. Ringing in the ears had been present intermittently for a week prior to this time. Throughout his life he had had repeated attacks of sharp pains in the abdomen, short in duration and with no relation to meals or defecation.

The past history included tonsillitis, rheumatic fever, scarlet fever and measles. These diseases had no known sequelae. Four years prior to the illness in question he was said to have had meningitis, but the condition was later diagnosed as encephalitis. One year later he complained of failing vision, which was thought to be due to arteriosclerosis.

The patient was poorly nourished, with an apparent right facial paralysis and defective speech. Spastic paralysis of the right arm and flaccid paraplegia with anesthesia of the legs and decreased sensation up to the umbilicus were present. The blood pressure ranged from 250 systolic and 120 diastolic to 274 systolic and 140 diastolic; the temperature was 99.6 F., and the pulse rate, 100. Ophthalmoscopic examination revealed marked arteriosclerosis of the retinal vessels and evidences of old retinal hemorrhage. Vision was absent in the left eye and was only 2/5 in the right. The heart was enlarged to the left.

The urine contained casts, erythrocytes and leukocytes. The red blood count was within normal limits, while the white count varied from 13,000 to 15,000. The spinal fluid was normal. Phenolsulphonphthalein excretion after intramuscular injection was from 25 to 30 per cent in two hours. Blood cultures before death showed a growth of Bacillus coli-communior.

On May 24, generalized convulsions suddenly developed, the patient vomited, had incontinence of feces and died.

Postmortem Examination.—The heart weighed 500 Gm. All of the valves were essentially normal. The maximum thickness of the wall of the left ventricle was 30 mm.

Thirty per cent of the intima of the right coronary artery and less of the left showed yellow thickening. Atherosclerosis involved from 95 to 100 per cent of the intima of the aorta below the renal arteries. The vertebral and basilar arteries and also the branches of the circle of Willis showed marked yellow thickening of the intima and stood wide open when cut.

The right kidney weighed 210 Gm. The capsule stripped rather easily, leaving a fairly smooth surface with reddish-brown, slightly elevated areas from pinpoint size to that 12 by 30 mm.; several of these had yellow centers. Numerous red bands from 1 to 2 mm. in width extended through the entire renal cortex. Everywhere the normal cortical markings were absent or indistinct. The left kidney answered essentially to the same description as the right.

The brain was sectioned in the coronal plane and showed areas of yellow softening as follows: (1) immediately anterior to the optic chiasm and in the center of the corpus callosum, 5 by 6 mm.; (2) in the head of the left caudate nucleus, involving about one-half the width and two-thirds the length of the left internal capsule, 8 by 15 mm.; (3) in the plane just anterior to the cerebral peduncles, involving the left optic thalamus, the internal capsule and a part of the lenticular nucleus (both putamen and globus pallidus), 7 by 15 mm.; (4) in the plane immediately posterior to the cerebral peduncles, in the white matter just lateral to the lenticular nucleus, 5 by 6 mm.

Near the lower pole of the left kidney and attached to it by means of fibrous tissue and blood vessels was a round, well encapsulated mass 4 cm. in diameter. Its cut surface was moist and pale yellowish brown. A grating sensation was felt when a knife-blade was scraped over it. A cord of tissue 5 mm. in diameter extended from this mass of tissue to the left testicle.

The gallbladder contained about one hundred round black stones from 1 to 2 mm. in size. Its wall measured from 2 to 5 mm. in thickness.

The remaining organs showed little or no gross pathologic change.

The anatomic diagnosis was: multiple areas of softening in the brain; organized hemorrhagic softening in the posterior columns of the lumbar segments of the spinal cord; ganglioneuroma of the region of the left kidney; concentric hypertrophy of the heart; arteriosclerosis of the coronary arteries and of the arteries at the base of the brain; moderate thickening of the aortic and mitral

Fig. 1.—Photomicrograph of lower lumbar cord showing area of softening in posterior columns and the masses along each posterior nerve root.

valves; atheromatosis of the aorta; arteriosclerotic contracted kidneys; acute focal (descending) purulent and hemorrhagic nephritis; acute hemorrhagic pyelitis and cystitis; slight bilateral bronchopneumonia; bullous emphysema of the right lung; chronic cholecystitis, and cholelithiasis.

Microscopic Examination.—Microscopic examination of the various organs confirmed the anatomic diagnosis. Sections of the left testis revealed no mature spermatozoa. The smaller arteries and the arterioles in all organs examined had thickened hyaline walls and narrowed lumens. This change was most marked in the vessels of the kidneys, brain and spinal cord.

Some of the ganglion cells of the anterior horns in the lower portion of the spinal cord stained diffusely with hematoxylin, and the nuclei were indistinct. Occupying the central part of the posterior portion of the cord and close to the central canal, there was a fairly well circumscribed, pale, oval mass (fig. 1). The central part of this mass was necrotic and composed of granular material irregularly distributed in a fine fibrillar meshwork. Near one margin there was an area of hemorrhage. In the periphery of the mass there were numerous large round cells filled with brownish-yellow pigment. Outside the spinal cord along the posterior nerve roots were two rounded nodules about the size of the lower power field of

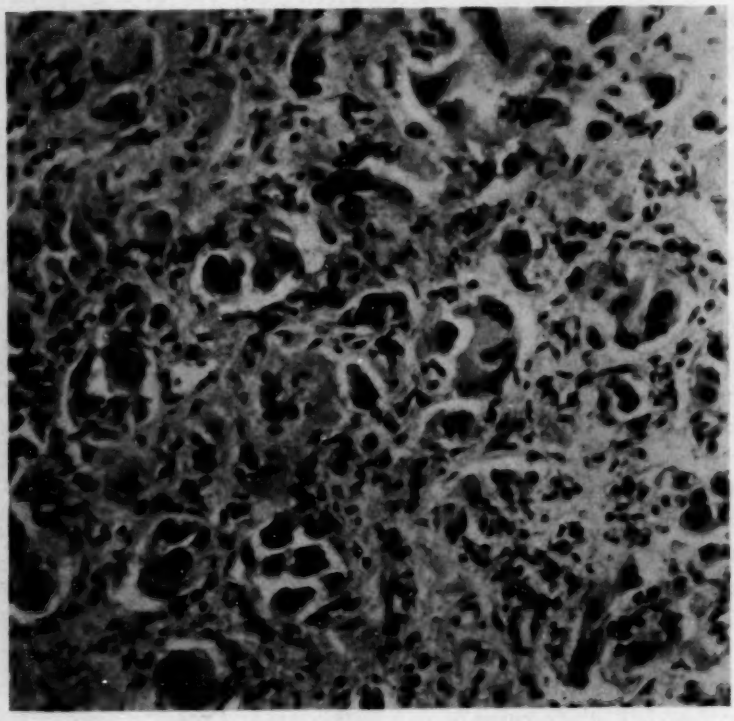

Fig. 2.—Photomicrograph of the tumor showing the various cell types described in the text; × 190.

a microscope. The central portion of one of these nodular masses was necrotic and contained brownish-yellow, granular pigment, much of which was intracellular. The peripheral portion of this mass was composed of round and elongated cells with a fibrillar network. The mass was enclosed in a sort of capsule, composed in part of connective tissue and along one side of what appeared to be nerve fibers. The nodule on the opposite posterolateral portion of the cord was composed of small round and oval cells in an abundant intercellular fibrillar material. The histologic picture of this organized hemorrhagic softening suggested an approximate age of 4 weeks.

The tumor near the left kidney was surrounded by a thick capsule of connective tissue from which septums passed into its substance. The parenchymatous elements

of the tumor consisted of cells, to be described later, which for the most part were arranged in the form of indistinct nests and cylindric cords (fig. 2). However, an occasional cell could be found isolated. The stroma consisted of connective tissue; some of it contained collagen but most of it was argentophil. Numerous thin-walled and malformed blood vessels coursed throughout the tumor. In some of the vessels the intima showed a moderate degree of fibrosis, while in others the lumens had been practically obliterated. One vessel contained a calcified thrombus. The aforementioned nests of cells were composed of three general types. The less numerous type of cell had a rather compact nucleus and a small amount of cytoplasm. In the second type the nucleus stained less deeply and was almost vesicular, while the cytoplasm was more abundant. The third group of cells, which were in the majority, resembled somewhat those of a spinal ganglion. Generally they were multipolar, and each contained one or more large nuclei. The chromatin material was arranged in fine granules and skeins, or infrequently was collected for the most part in one or more nucleoli. Generally two or more of the cells or infrequently a single cell was enclosed in a capsule of argentophil connective tissue. The nerve fibers within the tumor were nonmedullated.

The cord of tissue which connected the tumor with the left testicle consisted chiefly of many blood vessels in a fibrous stroma. The intima of some of the arteries had undergone marked fibrosis.

COMMENT

Ganglioneuromas arise from cells which migrate from the neural crest during embryonic life. These undifferentiated sympathogonia may form mature chromaffin tissue or they may give rise to sympathetic ganglion cells. At any point in the process of differentiation of these cells, tumors may arise. The cellular architecture of the tumors can therefore be representative of any of the developmental stages through which the cells pass in their process of maturation. Cases of ganglioneuroma and paraganglioma occurring in the region of the suprarenals have been reported from time to time. Bigler and Hoyne,[1] in 1932, reviewed the literature on ganglioneuroma and collected reports of ninety-seven cases. Haven and Weil[2] have since added a report of a case of multiple ganglioneuroma. Eisenberg and Wallerstein[3] collected reports of fifty-three cases of paraganglioma and reported one of malignant paraganglioma arising from the suprarenal medulla. Oppenheimer and Fishberg,[4] in 1924, could find no records of ganglioneuroma associated with hypertension. A review of the literature since 1924 likewise failed to reveal such an association.

Paraganglioma, on the other hand, especially that originating in the suprarenal glands, has been found associated with hypertension without

1. Bigler, J. A., and Hoyne, Archibald: Am. J. Dis. Child. **43**:1552, 1932.
2. Haven, Hale, and Weil, Arthur: Arch. Path. **13**:713, 1932.
3. Eisenberg, A. A., and Wallerstein, Harry: Arch. Path. **14**:818, 1932.
4. Oppenheimer, B. S., and Fishberg, A. M.: Arch. Int. Med. **34**:631, 1924.

any other discoverable etiologic factor (Mayo,[5] Oppenheimer and Fishberg,[4] Pincoffs,[6] and Vaquez, Donzelot and Geraudel [7]).

Some paragangliomas are composed of epinephrine-bearing tissue, while ganglioneuromas do not contain such elements. One may conclude, therefore, that in spite of the origin of these two tumors from a common primitive type of cell, when hypertension is associated with ganglioneuroma it is merely coincidental. It is believed that the hypertension in this case can best be explained on the basis of the renal and generalized vascular changes.

SUMMARY

A case of hypertension in a young man is reported. A small ganglioneuroma, histologically moderately mature, was found in the retroperitoneal region, near the left kidney.

Marked arteriosclerosis was present in the kidneys, brain and spinal cord. The brain and spinal cord showed multiple areas of hemorrhagic softening. There was moderate arteriosclerosis in the heart with mild involvement of the arterioles of the lungs, liver, suprarenal glands, pancreas, intestines and skeletal muscles. The left testis was maldeveloped.

Although hypertension not otherwise explainable has been observed associated with a type of tumor embryologically related to the tumor in this case, the high blood pressure in this patient can probably be explained best on the basis of the vascular and renal changes. The presence of the ganglioneuroma was most likely only coincidental.

5. Mayo, C. H.: J. A. M. A. **89**:1047, 1927.
6. Pincoffs, M. C.: J. A. M. A. **93**:63, 1929.
7. Vaquez, H.; Donzelot, E., and Geraudel, E.: Presse méd. **37**:169, 1929.

EXAMINATION OF PATHOLOGIC TISSUE BY FILTERED ULTRAVIOLET RADIATION

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AND
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Ultraviolet rays have been used extensively in many scientific fields. In the medical branches considerable application has been made in clinical dermatology. Ultraviolet radiation has been applied, to some degree, in the gross examination of normal tissues, but in the investigation of pathologic material it has had limited application.

The source of ultraviolet radiation may be a mercury vapor, carbon arc or cold quartz lamp. In our studies we used a mercury vapor arc lamp. In order to procure a maximal fluorescent effect, the radiation, consisting of longer and shorter waves, should be filtered through a nickel oxide filter. This permits the selection of waves ranging from 300 to 400 millimicrons in length (with the greatest spectral intensity at 366 millimicrons). The examination of pathologic material must be performed either in a dark room or in a dark hood. Water-washed specimens, either fresh or fixed in a dilute solution of formaldehyde, U. S. P. (1:10), will, when examined by ultraviolet radiation, emit secondary visible rays; this phenomenon is called fluorescence. If a specimen has been fixed in a dilute solution of formaldehyde for five or more days, it loses the optimal fluorescent effect; under such circumstances the removal of a thin slice of tissue will restore the maximal fluorescence.

The study of normal tissues by filtered ultraviolet radiation is reviewed thoroughly in Danckwortt's [1] monograph. Knowledge of the fluorescence of normal tissue is helpful in undertaking the investigation of pathologic tissue. Compact mature cortical bone fluoresces a light blue to a yellow-white, depending on compactness; this is apparently related to the ratio of inorganic to organic substances. Articular cartilage in the young fluoresces a uniform light blue, contrasting strongly with the opaque yellow-white of articular cartilage of adults. Subcutaneous or abdominal fat emits a clear yellow fluorescence. Muscle varies from a light tan to a dark brown, probably depending on the blood content. The various connective tissues fluoresce differently,

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From the Laboratory Division, Hospital for Joint Diseases.
Aided by the Emanuel Libman Fund.

1. Danckwortt, P. W.: Lumineszenz-Analyse im filtrierten ultravioletten Licht, Leipzig, Akademische Verlagsgesellschaft, 1929.

depending on consistency and cellularity; the more cellular connective tissues fluoresce purple-brown, whereas dense acellular connective tissue, such as tendon, fluoresces white.

As stated, little work has been done with pathologic tissues. Körbler [2] recently reported on the examination of three pathologic breasts; Kramer [3] described the appearance of four specimens; Policard [4] studied an experimental rat sarcoma and noted that the center of the tumor was a brilliant red (it was surrounded by a narrow zone of dark violet, which was again encircled by a white periphery). This red fluorescence is characteristic of hematoporphyrin; its presence in tumors is considered to be a result of bacterial infection. Körbler [2] mentioned the red fluorescence of carcinomatous ulcers, superficially located. A red fluorescence has been noted in a wide variety of conditions, and is not specifically indicative of tumor.

Our own experience includes a study of over five hundred specimens from postmortem and surgical material. In most, an opportunity of correlating the gross and microscopic findings with the fluorescent appearances was afforded. Our interest was centered mainly on the examination of tumors, especially of bone.[5]

The examination of any tissue or organ by filtered ultraviolet radiation resolves that tissue or organ into its constituent elements. It is a macroscopic method of differentiating the various components of a specimen through variation in fluorescence. The colors evoked are not necessarily specific, since tissues of various natures may sometimes emit approximately the same fluorescence (both tendons and mature bone fluoresce in shades of white). This is an important point and should be stressed. However, after experience, a particular type of tissue may be usually recognized by its fluorescence with ease, and minor variations therefrom may be readily interpreted. The variations in color probably depend on both inorganic (as in bone) and organic (as in fat) constituents, and on both intracellular (as in carcinomas) and extracellular (as in tendon) material. In this connection, variations in the inorganic content of nuclei and of cytoplasm in different carcinomas were reported by Scott and Horning.[6]

Furthermore, with filtered ultraviolet radiation areas not well demarcated under natural light are clearly visualized. Areas which

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2. Körbler, J.: Strahlentherapie **41**:510, 1931; **43**:317, 1932.

3. Kramer, K.: Virchows Arch. f. path. Anat. **274**:215, 1929.

4. Policard, A.: Compt. rend. Soc. de biol. **91**:1423, 1924; Bull. d'histol. appliq. à la physiol. **5**:266, 1928.

5. This formed the basis of an exhibit at the Post-Graduate Fortnight at the Academy of Medicine of New York, 1932.

6. Scott, G. H., and Horning, E. S.: Am. J. Path. **8**:329, 1932. Scott, G. H.: Science **76**:148, 1932.

appear uniform both to palpation and to unaided vision will often show on examination under ultraviolet radiation a variegated appearance, presenting several distinct colors. Thus small nodules, ordinarily invisible, become apparent.

The results of our examinations, covering many tissues and organs, can be briefly summarized. In regard to the intestinal tract, we find that fluorescence of the serosa varies from purple to deep brown, depending on the amounts of blood and of exudate; the submucosa and muscularis (depending probably on their cellularity) fluoresce various shades of purple and white. A cellular tumor that has extended into the muscular layer of the stomach or rectum will fluoresce from a purple to a deep brown, against the white background of the fibrotic muscular coat. Collections of cholesterol in the wall of an inflamed gallbladder appear golden yellow, even if they are not readily perceptible in natural light.

Similarly, the genital organs will fluoresce from purple to brown, depending on the type of tissue; a soft myomatous nodule of the uterus, containing almost imperceptible hyalinized foci, fluoresces brown with blue-white spots. The ovary often shows cysts which in natural light are not to be identified, but their luteal origin is revealed by the yellow fluorescence. The breast, like other organs, normally fluoresces white, brown or purple, depending on its constituent tissues. A medullary carcinoma in a zone of fibrous tissue appears purple against white. In many instances metastatic foci in lymph glands fluoresce the same color as that of the primary growth. The thyroid fluoresces various shades of brown, depending on the amount of colloid and on the vascularity.

Of the large number of specimens examined, two are described in some detail to show the usefulness of examining tissue with ultraviolet radiation. The first specimen was a breast with a carcinoma. In figure 1 *A*, the tumor is uniformly white, and it is surrounded by contiguous fatty tissues. Under filtered ultraviolet radiation, the area of the tumor, as observed in figure 1 *B*, is definitely divided into two portions. The upper is hazy blue and the lower, white. Below this white region there is a zone containing numerous blue areas. Microscopically, the upper portion is medullary adenocarcinoma, while the lower portion is quite scirrhous. The smaller blue areas are foci of carcinoma metastases. Gross infiltration of the skin by carcinoma is also observed in figure 1 *B*. In another breast, a small tumor nodule in the fat, which in natural light looked much like ordinary fat, was distinctly outlined as a bluish-purple nodule under the radiation.

The second specimen (fig. 2 *A*) was from the upper part of a femur affected by Paget's disease. Under radiation, as observed in figure 2 *B*, the white area extending from the diaphysis into the neck represents the

Fig. 1 *A*.—Adenocarcinoma of the breast.

Fig. 2 *A*.—Upper part of a femur (Paget's disease).

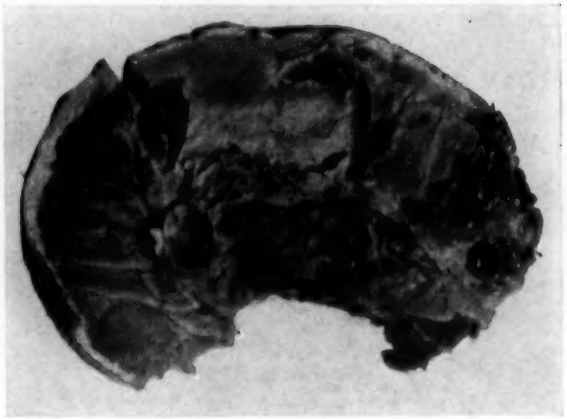

Fig. 1 *B*.—Same specimen shown in figure 1 *A* as seen under filtered ultraviolet radiation.

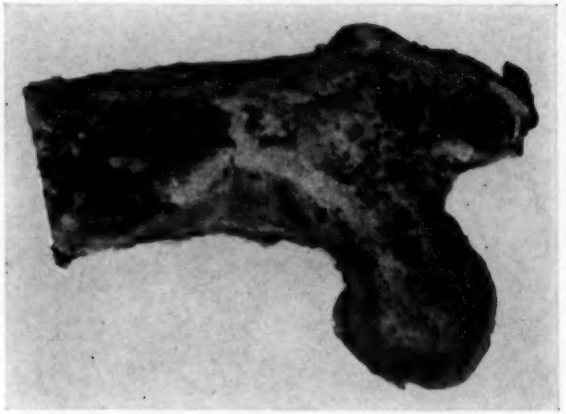

Fig. 2 *B*.—Same specimen shown in figure 2 *A* as seen under filtered ultraviolet radiation.

MUSEUM OF MEDICINE

most sclerosed and therefore, histologically, the most compact bone. The less sclerosed bone is blue. This was composed of areas showing the mosaic and separated by soft tissue spaces. The most superficial bone, brown-blue in color, was the most newly formed and contained the least calcium. This specimen illustrates unusually well the deposition of periosteal bone in Paget's disease. The large blue osteophytes are due to proliferation and formation of new bone.

CONCLUSION

Filtered ultraviolet radiation aids the surgeon and the pathologist in detecting small areas of disease. These may be imperceptible to the naked eye. It makes possible a gross examination in colors without the use of stains for selective differentiation. As the fluorescence probably depends on the chemical constituents in the nuclei, cytoplasm and intercellular substance of the tissues, we have been unable to find a specific correlation between the fluorescent reaction and the pathologic diagnosis. Nevertheless, the method resolves the tissue into its constituent elements by adding another "color octave" to our range of vision.

NORMAL VARIABILITY IN WEIGHT OF THE ADULT HUMAN LIVER AND SPLEEN

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MINNEAPOLIS

INTRODUCTION

In a study on the disease conditions in which the liver and the spleen are hypertrophied, Barron and Litman [1] assumed that any adult liver weighing 2,200 Gm. or more and any spleen weighing 300 Gm. or more were hypertrophied. They stated: "The basis for this arbitrary choice of figures is the fact that livers and spleens generally become palpable when they reach such proportions." At the time of their study, Dr. Barron realized that in estimating these values they had failed to take into consideration the probable changes with age, the well recognized sex differences or the general effect of disease on organs not involved in the disease process.

Perusal of the anatomic data on the weights of organs clearly indicates that the organs of the female are usually smaller than those of the male, that most organs decrease in weight during senility, that an organ may increase, be stationary or decrease in weight from early adult life to middle age, that the descriptions from different sources of age changes in early adult life for a given organ are frequently contradictory, and that inanition from any cause tends to reduce the weight of most organs.

In 1906, Vierordt [2] summarized most of the early data. Reviews of the literature and additional data on the weights of organs, including the liver and the spleen, are given by Greenwood,[3] Greenwood and Brown,[4] Bean and Baker,[5] Bean,[6] and Pearl and Bacon.[7] Jackson [8] summarized the data on the effects of inanition and malnutrition on

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From the Institute of Child Welfare and Department of Anatomy, University of Minnesota.

1. Barron, M., and Litman, A. B.: Arch. Int. Med. **50**:240, 1932.

2. Vierordt, H.: Anatomische, physiologische und physikalische Daten und Tabellen, ed. 3, Jena, Gustav Fischer, 1906.

3. Greenwood, M., Jr.: Biometrika **3**:63, 1904.

4. Greenwood, M., Jr., and Brown, J. W.: Biometrika **9**:473, 1913.

5. Bean, R. B., and Baker, W.: Am. J. Phys. Anthrop. **2**:1 and 167, 1919.

6. Bean, R. B.: Am. J. Phys. Anthrop. **9**:293, 1926.

7. Pearl, R., and Bacon, A. L.: Johns Hopkins Hosp. Rep. **21**:297, 1924.

8. Jackson, C. M.: The Effects of Inanition and Malnutrition Upon Growth and Structure, Philadelphia, P. Blakiston's Son & Co., 1925; Arch. Path. **7**: 1042, 1929; **8**:81 and 273, 1929.

all organs. In his careful review, he stated that most of the data indicate that with inanition there is a marked decrease in the weight of the liver of both man and animals, which tends to be relatively greater than the loss in total body weight. In extreme emaciation the spleen is greatly reduced in weight, the relative loss being twice as great as that of the total body weight, but in early stages of inanition the reduction is slight and difficult to establish because of the great normal variability of the weight of the spleen.

Practically, in the general run of necropsies on adults, the pathologists would probably recognize the reduction in the size of the organ due to old age and hence exclude senile organs from their estimates of normal weight, but they would constantly accept as normal the organs reduced in weight by inanition, thus underestimating both the mean value and the upper limit of normal variation in weight. This source of error is inherent in most pathologic data, since most people are ill for some time before death. Pearl and Bacon [7] discussed this serious limitation of hospital records of necropsies and stated that the ideal subjects for establishing normal standards would be those killed by violent accidents. Since the staff of the department of pathology of the University of Minnesota perform all coroner's autopsies in Hennepin County, which, according to Bell,[9] amount to about 200 a year, the records of the department contain considerable data on the weights of organs from persons killed by violent accidents.

In view of these various considerations, at Dr. Barron's request,[10] I undertook to establish more exactly from these data on accidental deaths the probable upper limit of normal weight of the liver and the spleen, including the age and sex differences and, as a necessary step, the normal variability in weight of the liver and the spleen. Dr. Bell granted the free use of all the records of the department of pathology.

CHARACTER AND SELECTION OF DATA

Of the 9,886 necropsies performed on adults 20 or more years of age from January, 1920, to July, 1931, inclusive, death was due to accidental causes, such as fractured skulls, gunshot wounds, suffocations and poisonings in 1,791, or 18 per cent of the subjects. Records of 175 necropsies were not usable because of incomplete information as to age, body length or weight of the liver and spleen. In addition, 34 records for persons 80 years or more of age were omitted because they were too few for statistical analysis. Of the remaining 1,582 subjects, 1,266 were males and 316 females. Information as to race

9. Bell, E. T.: J. A. M. A. **90**:896, 1928.

10. Financial aid for this study was given by a grant made to Dr. Barron of the department of medicine by the Research Fund of the Graduate School of the University of Minnesota.

or nationality was given consistently only when the race could be recognized by pigmentation. According to this criterion, the subjects were predominantly Caucasians, since there were only 31 Negroes and 4 Chinese.

The routine procedure in performing a necropsy is first to open the abdomen and inspect its contents, and then to open the thorax and inspect its contents; next the thoracic organs are removed, and finally, the abdominal organs. Usually the spleen is removed before the liver. If an assistant is present, which is generally the case at coroner's necropsies, the organs are weighed immediately after removal; otherwise they are put aside until the end of the examination, when all organs are weighed. When the autopsy is done at the city morgue, the organs are weighed accurately to 1 Gm. on a counterbalance pan scale. When the examination is conducted in an undertaking establishment, hospital morgue or home, the spleen is weighed on a portable spring balance scale reading to 10 Gm. and the liver is weighed on one reading to 25 Gm. With use the spring stretches, so that the scales tend to read too high. More than 95 per cent of the postmortem examinations are made at the city morgue.

In cases of deaths from accidents, the interval between the time of injury and of death may vary from a few minutes to several weeks. If this period is prolonged, more or less malnutrition usually occurs, which, according to Jackson's summary,[8] reduces the size of the organs, and secondary infections set in, which may either indirectly reduce the weight of the organs by affecting nutrition or directly enlarge the organs by cloudy swelling. To avoid including the weights of organs materially affected either by malnutrition or by secondary infections, I arbitrarily divided the data into two major groups, namely, for persons (I) ill less than twenty-four hours, and (II) ill one day or more. This time limit, first used by Hammar,[11] is the same that I used in a similar analysis of the weight of the thymus,[12] in which the weights were significantly lowered when the subjects had died within from one to seven days after the onset of the illness. Since the thymus is probably more sensitive to inanition than any other organ,[8] this time limit may be assumed to be adequate for eliminating organs which have been affected by inanition and is probably short enough to avoid any marked effects of secondary infections.

While most of the persons killed by accidents were able to work up to the time of injury, some of them were known to be sick or had a

11. Hammar, J. A.: Arch. f. Anat. u. Entwcklngsgesch., supp., 1906, p. 91; Ztschr. f. mikr.-anat. Forsch., supp., vol. 6, 1926; supp., vol. 16, 1929.

12. Boyd, E.: Am. J. Dis. Child. **43**:1162, 1932

latent disease process, which was found at necropsy. As a result, two secondary categories were set up: (*A*) no additional disease, and (*B*) additional disease, as indicated by signs or symptoms of disease present before injury or by evidence of disease found post mortem. When infectious processes were apparently secondary to injury, they were classified as (*A*) no additional disease. Signs of old healed infections, such as pleural adhesions, were not considered disease processes. Also, since arteriosclerosis was found in many subjects over 50 years of age, it was accepted as part of the normal age changes in the body. These two decisions were made after plotting all weights of both organs against age and indicating which ones came from subjects with arteriosclerosis or old healed infections. As judged by inspection of the scatter diagrams, these conditions did not affect the weights of either organ.

Many of the protocols contained the diagnosis of alcoholism, and 98 subjects died of acute alcoholism. Unfortunately, the absence of a statement concerning alcohol does not mean that it was not used, and, on the other hand, the diagnosis of alcoholism gives no index of the amount of alcohol consumed. After graphic analysis of the data, I came to the following conclusions:

When the diagnosis was acute alcoholism and there was no fatty degeneration of the liver, the case might be considered one of acute poisoning. When alcoholism was recorded in a death from an accident and the liver showed no fatty degeneration, the case was considered as a death from accident, i. e., (*A*) no additional disease. Finally, when either chronic alcoholism or a fatty liver was present, the case was considered one of (*B*) additional disease. As a matter of fact, when chronic alcoholism was diagnosed, fatty degeneration of the liver was almost always present.

The character of the agent causing death might materially affect the weights of both the liver and the spleen. Poisons which act directly on the central nervous system, such as strychnine, hydrocyanic acid and morphine, would not be expected to change the weight of either organ materially, while those which act by injuring the parenchymatous organs, such as compounds of mercury, arsenic and bismuth, and the strong acids or caustics, such as phenol, lye and compound solution of cresol, would probably materially affect the weights of the liver and the spleen. Hence the cases of poisonings were separated into these two general groups, and burns were arbitrarily added to the latter group.

When a person is killed by violence, excessive loss of blood frequently occurs and is often the cause of death. Preliminary tests indicated that this loss of blood materially reduced the weights of both the

liver and the spleen.[13] The diagnosis of gross hemorrhage was made when the protocol contained such findings as rupture of the liver, spleen, heart, large blood vessels, hemoperitoneum and hemothorax.

Finally, all organs, and especially the spleen, are apt to be congested in subjects killed by electrocution, suffocation or drownings and carbon monoxide poisoning. This congestion was assumed to be within physiologic limits of the organs.

As a result of these considerations, the data within the two categories, (I) ill less than twenty-four hours and (II) ill one day or more, and their subdivisions, (*A*) no additional disease and (*B*) additional disease, were each again subdivided into (1) all accidents without gross hemorrhage, consisting of (*a*) trauma without gross hemorrhage, (*b*) electrocutions, suffocations and drownings, (*c*) poisoning by carbon monoxide, cyanide compounds, alkaloids and narcotics and (*d*) poisoning by alcohol, (2) trauma with gross hemorrhage and (3) poisonings by heavy metals, strong acids and caustics, and burns, as shown in table 1.

The 312 cases falling under the headings (I) ill less than twenty-four hours, (*A*) no additional disease, (1) accidents without gross hemorrhage, may be considered essentially normal subjects; hence a reasonable sample from which to establish standards of normal variability in weights of organs. The 489 cases falling under the headings (I) ill less than twenty-four hours, (*A*) no additional disease, (2) trauma with gross hemorrhage are equally normal subjects. They are comparable to the laboratory animal killed by a blow on the head and then bled by cutting the vessels of the neck, while the group I have considered normal is comparable in part, at least, to the laboratory animal killed by etherization.

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13. The marked effect of gross hemorrhage on these weights was found inadvertently. In the first sorting of the record cards, I had separated those cases with rupture of either the liver or the spleen, with the idea of excluding them from the normal data. Graphic analysis showed that the weights of these ruptured organs fell within the same range as the organs from other cases of trauma, but large numbers of them were in the lower part of the range. Also, if only the livers were ruptured, the nonruptured spleens from the same subjects tended to fall in the same part of the ranges as the weights of the ruptured spleens. The same relation held for the weights of ruptured spleens and nonruptured livers. When the traumatic cases without rupture of either liver or spleen were divided into those with and those without gross hemorrhage from other ruptured organs, the weights from cases without any gross hemorrhage tended to fall above the weights from those with hemorrhage. Moreover, the weights from cases of hemorrhage did not seem to vary according to source of hemorrhage, i. e., the livers and spleens themselves or other organs. Hence it was concluded that massive hemorrhage from any part of the body reduced the weight of the liver and spleen as much as hemorrhage from the organs themselves.

After discussing this problem with me, Dr. Charlotte Van Winkle [14] carried out a comparison of both the weights of the liver and the spleen between guinea-pigs killed by a blow on the head and those killed by etherization. Her findings, which will be published elsewhere, show that the liver is significantly smaller in the group that was bled, while there is no demonstrable difference between the weights of the spleen in this group bled and the group that was killed by etherization. The latter finding is not in agreement with the findings for man, in whom both organs are reduced by gross hemorrhage, as will be demonstrated later. A possible physiologic explanation is that the spleen contracts in the struggling etherized animal, thus emptying the spleen of blood as effectively as by bleeding by cutting the large vessels while the heart

TABLE 1.—*Case Incidence According to Type of Accident Causing Death, Duration of Illness, Presence or Absence of Disease and Sex*

	I. Ill Less Than 24 Hours (1,074 Cases)						II. Ill 1 Day or More (508 Cases)						
	A. No Additional Disease			B. Additional Disease			A. No Additional Disease			B. Additional Disease			
	Male	Female	Both Sexes	Male	Female	Both Sexes	Male	Female	Both Sexes	Male	Female	Both Sexes	Totals
(1) All accidents without gross hemorrhage	239	73	312	121	41	162	145	30	175	149	38	187	836
(2) Trauma with gross hemorrhage	406	83	489	58	12	70	79	13	92	27	7	34	685
(3) Poisonings by heavy metals, burns, etc.	18	5	23	12	6	18	9	5	14	3	3	6	61
Totals	663	161	824	191	59	250	233	48	281	179	48	227	1,582

is still beating. Further consideration of this problem will be taken up by Dr. Van Winkle in her article.

Since most deaths from disease are not associated with gross hemorrhage, the nonhemorrhagic group has been used for establishing normal standards of variability in the weight of the liver and spleen.

ANALYSIS OF DATA

When the weights of the liver and spleen from the nonhemorrhagic group just selected as normal are plotted for both sexes against age (charts 1 and 2), the weights of the liver in both sexes seem to increase slightly from 20 to 50 years of age, especially in the upper range of weight, then to decrease, and the livers of the males tend to be larger than those of the females. On the other hand, the weights of the spleen in both sexes appear to decrease both in amount and variability from 20 to 50

14. Pathologist and Director of Laboratory, Glen Lake Sanatorium, Oak Terrace, Minn.

years, and the weights of the spleen in the females do not appear to be materially smaller than those of the males.

The central trend in weight of these organs could be represented by various methods. The most common procedure in current use is to average the weights for given age periods, then to pass a trend line through these averages by a point to point line drawn in from average

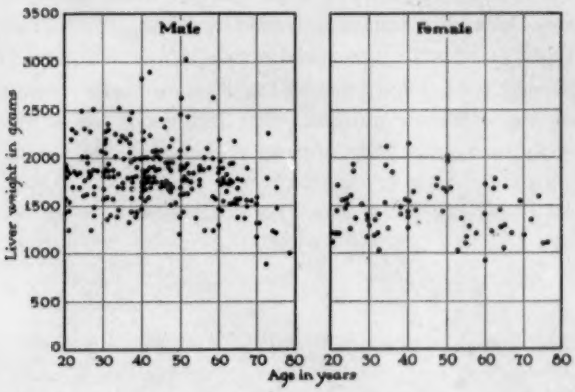

Chart 1.—Scatter diagrams of the weights of the livers with age from normal males and females, i. e., those in the group (I) ill less than twenty-four hours, (*A*) no additional disease, (1) all accidents without gross hemorrhage.

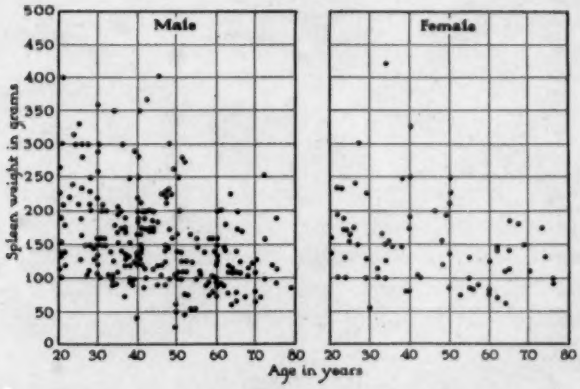

Chart 2.—Scatter diagrams of the weights of the spleen with age from normal males and females, i. e., those in the group (I) ill less than twenty-four hours, (*A*) no additional disease, (1) all accidents without gross hemorrhage.

to average, or by a smooth curve drawn by inspection to the averages, or by fitting a line to the averages by the method of least squares, or, for the weights of the spleen which appear to have approximately a straight line trend with age, by fitting the regression line by the Pearsonian correlation technic. The variability around these trends could be measured in terms of one and two standard deviations from the

mean weights for each age period or from the regression line for all age periods, so that the middle two thirds of the weights would fall between plus and minus one standard deviation and the middle 95 per cent of the weights between plus and minus two standard deviations. Actually, these methods were first applied to these data, but it was found that the weights of both organs, and especially those of the spleen, like those of the thymus,[12] were so skew that the lower two standard deviations line fell below all the weights, instead of 2.5 per cent of the weights falling below it.[15]

Construction of Standards of Normal Variability in the Weight of the Liver and the Spleen.—As a result of these findings, as in the analysis of the weights of the thymus, the medium weights,[16] or 50 percentiles of weight for 10 year age periods, were used to represent the central trend; the weight range from the 25 to the 50 percentiles, the middle 50 per cent of the weights, and the weight range from the 10 to the 90 percentiles, the middle 80 per cent of the weights. To these were added the 2.5 and the 97.5 percentiles as the probable lower and upper limits of normal variability.[17]

The designated percentiles were found for the weights of both organs in each 10 year age group for both sexes by the graphic method given by Yule.[18] The values for each percentile along with the minimum and maximum weights for the liver are given in table 2, and for the spleen in table 3. Whenever there were marked irregularities from age period to age period, the values were smoothed by one application of three point smoothing.[19]

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15. When the weights were plotted on a six-zone standard based on plus and minus one and two standard deviations, the Chi-square and *P* for the difference between the observed and theoretical number in each zone were 14.79 and 0.01 for the liver and 27.21 and 0.000057 for the spleen.

16. On the average, in these data the median weight of the liver is in males 24 Gm., or 1.4 per cent below the mean weight, and in females 48 Gm., or 3.3 per cent. The median weight of the spleen is on the average in males 13 Gm., or 8.3 per cent below the mean weight, and in females 10 Gm., or 6.8 per cent. The means, standard deviations and correlations of liver and spleen, liver and height and spleen and height will be published in a subsequent report.

17. These arbitary limits were chosen because they represent essentially the same level of probability, i. e., 0.025, commonly used as the dividing line between probably significant and nonsignificant deviations within a normal distribution. Hence, the 97.5 and 2.5 percentile lines of these skew distributions correspond approximately to plus and minus three probable errors, or two standard deviations from the mean of normal distributions.

18. Yule, G. U.: An Introduction to the Theory of Statistics, ed. 9, London, Charles Griffin & Co., 1929.

19. The weight for the calculated 2.5 percentile can be less than the observed minimum weight when there are few weights and several are near the minimum weight, so that the curve drawn in by inspection extends beyond the minimum weight. The same principle applies when the weight for the 97.5 percentile is larger than the observed maximum weight.

Graphic charts giving the variability for the total age period for each organ and sex were constructed by plotting the weights for the 97.5, 90, 75, 50, 25, 10 and 2.5 percentiles of each 10 year age interval against the mid-age of the interval and by joining all 97.5 percentiles with a continuous line, all 90 percentiles with another continuous line, and so on for the 75, 50, 25, 10 and 2.5 percentiles, respectively.

TABLE 2.—*Percentiles of Weight for the Normal Liver* [19]

Age Interval, Years	Number of Cases	Maximum Weight, Gm.	Percentiles of Weight in Grams							Minimum Weight, Gm.
			97.5	90	75	50	25	10	2.5	
Males										
20 to 29	38	2,500	2,480	2,300	2,000	1,820	1,640	1,420	1,300	1,235
30 to 39	54	2,515	2,520	2,310	2,030	1,830	1,640	1,490	1,370	1,327
40 to 49	58	2,900	2,600	2,290	2,030	1,840	1,670	1,510	1,350	1,470
50 to 59	39	3,020	2,570	2,100	2,000	1,840	1,640	1,510	1,350	1,200
60 to 69	37	2,400	2,420	2,070	1,890	1,740	1,580	1,420	1,320	1,300
70 to 79	13	2,263	2,140	1,860	1,640	1,380	1,180	1,020	900	900
Females										
20 to 29	19	1,920	1,900	1,720	1,560	1,440	1,280	1,140	1,080	1,114
30 to 39	14	2,120	2,040	1,820	1,620	1,460	1,320	1,200	1,080	1,023
40 to 49	11	2,130	2,100	1,910	1,690	1,440	1,290	1,180	1,220	1,250
50 to 59	11	2,000	1,990	1,870	1,700	1,430	1,260	1,140	1,010	1,020
60 to 69	13	1,780	1,880	1,780	1,560	1,380	1,150	1,050	910	925
70 to 79	5	1,595	1,760	1,600	1,380	1,180	1,100	1,040	1,000	1,100

TABLE 3.—*Percentiles of Weight for the Normal Spleen* [19]

Age Interval, Years	Number of Cases	Maximum Weight, Gm.	Percentiles of Weight in Grams							Minimum Weight, Gm.
			97.5	90	75	50	25	10	2.5	
Males										
20 to 29	38	400	364	318	250	194	144	116	96	90
30 to 39	54	360	356	281	220	172	131	106	86	75
40 to 49	58	400	327	234	187	144	112	86	65	75
50 to 59	39	280	285	229	172	135	106	84	61	25
60 to 69	37	225	243	205	147	113	94	74	61	60
70 to 79	13	255	234	188	136	108	90	74	66	65
Females										
20 to 29	19	300	300	255	205	165	130	95	65	65
30 to 39	14	420	310	258	200	162	118	85	63	55
40 to 49	11	325	293	252	195	142	102	80	65	80
50 to 59	11	250	273	227	182	135	95	77	67	75
60 to 69	13	284	230	198	160	113	87	78	68	61
70 to 79	5	175	195	175	140	110	95	78	70	90

The results are shown in charts 3 and 4, and the scatter of observed values against the standards constructed from them in charts 5 and 6. According to the construction of the graphs, 2.5 per cent of the weights of normal organs would be expected to fall both above the 97.5 percentile line and below the 2.5 percentile line, 7.5 per cent in the clear zones between the 97.5 and 90 and the 10 and 2.5 percentile lines, 15 per cent in the lightly shaded zones between the 90 and 75 and the 25 and 10 percentile lines, and 25 per cent in the heavily shaded zones between both the 75 and 50 and the 50 and 25 percentile lines.

According to these charts and tables, the liver of the male tends to increase from a median weight of 1,820 Gm. at 25 years to a median weight of 1,840 Gm. at 55 years and then to decrease 360 Gm., or 20 per cent, to a median weight of 1,480 Gm. by 75 years. The median

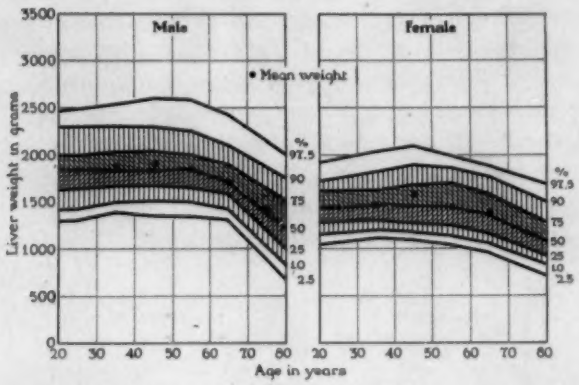

Chart 3.—Graphic standards of normal variability in weight of the liver of both the male and the female based on the data in chart 1. The percentage figures given at the side of each panel indicate the percentiles of weight. Fifty per cent of normal weights may be expected to fall in the heavily shaded zone, 80 per cent in the totally shaded zone and 95 per cent in the total zone limited by the 97.5 and the 2.5 percentile lines. For practical purposes, the last two percentile lines may be considered the usual upper and lower limits of normal variability in weight of the liver.

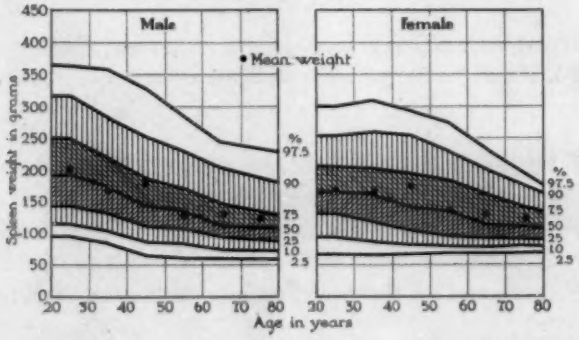

Chart 4.—Graphic standards of normal variability in weight of the spleen of both the male and female based on the data in chart 2. The percentage figures given at the side of each panel indicate the percentiles of weight. Fifty per cent of normal weights will be expected to fall in the heavily shaded zone, 80 per cent in the totally shaded zone and 95 per cent in the total zone limited by the 97.5 and the 2.5 percentile lines. For practical purposes, the last two percentile lines may be considered the usual upper and lower limits of normal variability in the weight of the spleen.

weight of the liver of the female fluctuates between 1,460 and 1,430 Gm. in the four decades from 20 to 60 years, then definitely decreases approximately 250 Gm., or 11 per cent, to 1,180 Gm. by 75 years. Thus, the liver of the male is from 200 to 400 Gm. heavier than the liver of the female, and the liver in both sexes is essentially stationary in weight from 20 to 55 years of age and then decreases in weight.

The variability in the weight of the liver, as illustrated by the various shaded zones, shows that on the average the middle 50 per cent of weights covers a range of 370 Gm. in the male and 360 Gm. in the female, the middle 80 per cent a range of 840 Gm. in the male and 660 Gm. in the female, and the middle 95 per cent a range of 1,190 Gm. in the male and 900 Gm. in the female. In relative terms, the 75 percentile line averages 15 per cent above the median line for males and

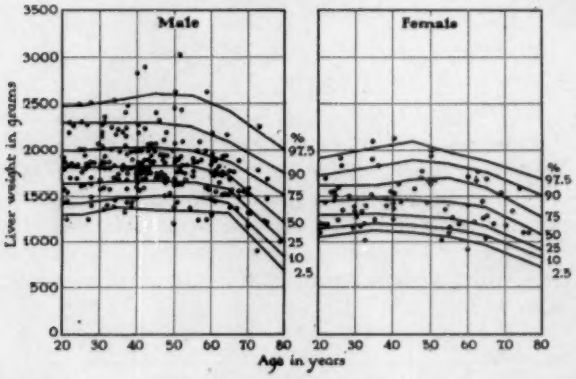

Chart 5.—Graph showing the weights of the liver from normal males and females, chart 1, plotted on the percentile standard, chart 3, constructed from these weights.

11 per cent for females, while the 25 percentile line averages 10 per cent below the median line for both sexes. The 97.5 percentile line averages 42 and 40 per cent above the median line, and the 2.5 percentile line 26 and 24 per cent below it. These findings show the marked skewness of the weights in both sexes and for all age periods.

In contrast to the liver, the spleen in both sexes tends to decrease throughout adult life. The median weight of the spleen of the male decreases 86 Gm., or 44 per cent, from 194 Gm. at 25 years to 108 Gm. at 75 years, and that of the female decreases 55 Gm., or 33 per cent, from 165 Gm. at 25 years to 110 Gm. at 75 years. There is no material difference between the median weights for the two sexes, except in the decade from 20 to 30 years, when the spleen of the male is 14 per cent heavier than that of the female. In the male the middle 50 per cent of

weights cover a mean range of 72 Gm., the middle 80 per cent a mean range of 156 Gm. and the middle 95 per cent a mean range of 227 Gm. In the female these ranges are 76 Gm., 146 Gm. and 156 Gm., respectively. Relatively, this variability is about twice that of the liver. In the male the 75 percentile line averages 28 per cent above the median weight, and the 25 percentile line averages 23 per cent below it; the 97.5 percentile line averages 111 per cent above the median weight and the 2.5 percentile line averages 49 per cent below. In the female the 75 and 25 percentile lines average 31 and 23 per cent above and below the median weight, respectively, and the 97.5 and 2.5 percentile lines average 94 and 47 per cent above and below it.

This great normal variability in the spleen, as estimated from these data, is probably due to the normal contractility of the organ. In data

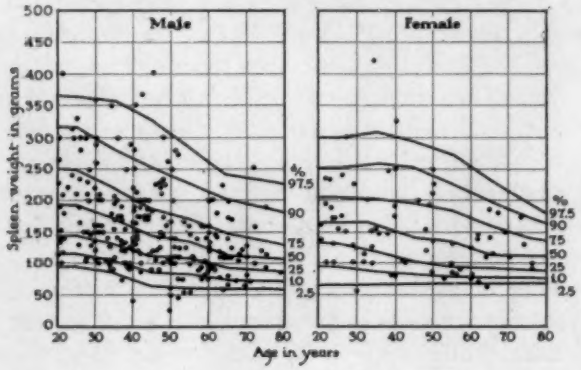

Chart 6.—Graph showing the weights of the spleen from normal males and females, chart 2, plotted on the percentile standard, chart 4, constructed from these weights.

from man, the state of contraction or dilatation cannot be controlled. As a result, the weights of the spleen from conditions known to cause contraction would tend to fall in the lower zones, and those from conditions which cause dilatation would tend to fall in disproportionate numbers in the upper zones of these standards. The latter possibility apparently occurred in the cases of poisoning from carbon monoxide, cyanide and other poisons, since 70 per cent of the weights in this group fell above the median line and only 30 per cent below it, in contrast to the expected 50 per cent on each side of the line.

That this disproportion is more than would be expected to occur by chance alone is demonstrated in the following test of the standard:

The goodness of the fits of the standards to the weights of both the liver and the spleen in the normal group, (I) ill less than twenty-four hours, (*A*) no additional disease, (1) all accidents without gross hem-

orrhage, and its subdivisions was tested by the Chi-square method. (The steps of this method are illustrated in table 6 for the comparison of the hemorrhagic group with the standard.) The fits for the total and all subgroups, except the weights of the spleen in cases of non-alcoholic poisoning, were found to be excellent, since the probability integrals, *P*, given in tables 4 and 5 were usually close to 0.90 and never less than 0.22, indicating that the differences could occur from chance alone from twenty-two to ninety times in a hundred.

Commonly, if *P* is 0.01 or less, i. e., chance could account for such a difference only once in a hundred times, it is assumed that the difference in that given comparison is not due to chance, and this difference is called significant. Hence, since *P* for the subgroup, poisonings by carbon monoxide, cyanide and other poisons, is 0.003, the 70 per cent of weights of the spleen above the median is significantly above the expected 50 per cent. Pathologists have the impression that relatively large spleens are found in cases of carbon monoxide poisoning. Because of this, I separated on the graphs the weights in cases of poisoning due to carbon monoxide from those due to other poisons. Both groups, however, tend to have a relatively high number of weights in the upper range of the normal variability. Hence, in the persons killed by the poisons which act on the central nervous system, the spleen tends to be larger than in persons killed by trauma. The liver of these same subjects shows no such tendency. Possibly, along with the paralysis of either respiratory or cardiac centers in the central nervous system, the vasomotor control of vessels to the spleen is stopped so that the spleen becomes dilated and filled with blood. On the other hand, in the various types of trauma, death has taken place with the spleen in any phase of its possible physiologic range from marked contraction to extreme dilatation.

On the whole, these standards may be assumed to be reasonable estimates of the central trend of the weights of the liver and the spleen with age and the variability around that central trend. The standard for males is more reliable for both organs than that for females, because the basic sample consisted of four times as many cases. Also the standards for the liver are more reliable than those for the spleen, because of the great physiologic variability of the spleen. The 97.5 and 2.5 percentile lines may be assumed to represent the probable limits of normal size, although two or three weights in every hundred in this series fell above and below these lines, and the same number would be expected in another identical series. However, the likelihood is great that the extreme upper and lower weights in this series actually came from subjects with some pathologic condition which was not recognized at postmortem examination or which did not leave adequate signs to be recognized by the customary methods of making the examinations.

TABLE 4.—*Comparison of the Weights of the Liver in the Various Subdivisions of the Normal Group (1) Ill Less Than Twenty-Four Hours, (A) No Additional Disease, (1) All Accidents Without Gross Hemorrhage, With the Normal Standard*

	Sex	Number of Weights	Percentage of Weights: Above 97.5 Line	Between the Percentile Lines: 97.5 to 90	90 to 75	75 to 50	50 to 25	25 to 10	10 to 2.5	Below 2.5 Line	n′	χ^2	P	Percentage of Weights: Above 50 Line	Below 50 Line
Percentage of weights expected			2.5	7.5	15	25	25	15	7.5	2.5				50	50
(1) All accidents without gross hemorrhage	Male	239	3	6	16	26	24	16	6	3	6	0.56	0.96	51	49
	Female	73	3	10	12	23	29	12	7	4	4	0.59	0.80	48	52
	Both sexes	312	3	6	15	26	25	15	6	4	6	0.08	0.99	50	50
(a) Trauma without gross hemorrhage	Male	102	4	1	15	27	20	17	12	4	6	7.18	0.22	47	53
	Female	44	5	11	13	23	23	11	9	5	4	0.55	0.80	52	48
	Both sexes	146	4	4	15	26	21	15	11	4	6	5.14	0.42	49	51
(b) Electrocutions, suffocations and drownings	Both sexes	45	4	7	20	13	31	20	3	2	4	3.80	0.26	44	56
(c) Poisoning by carbon monoxide, hydrocyanic acid, etc.	Both sexes	73	2	7	7	33	32	14	1	4	4	6.17	0.11	49	51
(d) Poisoning by alcohol	Both sexes	48	0	15	23	25	21	10	4	2	4	4.67	0.17	63	37

TABLE 5.—*Comparison of the Weights of the Spleen in the Various Subdivisions of the Normal Group, (1) Ill Less Than Twenty-Four Hours, (A) No Additional Disease, (1) All Accidents Without Gross Hemorrhage, With the Normal Standard*

	Sex	Number of Weights	Percentage of Weights: Above 97.5 Line	Between the Percentile Lines: 97.5 to 90	90 to 75	75 to 50	50 to 25	25 to 10	10 to 2.5	Below 2.5 Line	n′	χ^2	P	Percentage of Weights: Above 50 Line	Below 50 Line
Percentage of weights expected			2.5	7.5	15	25	25	15	7.5	2.5				50	50
(1) All accidents without gross hemorrhage	Male	239	2	8	15	26	23	15	8	3	6	0.55	0.96	51	49
	Female	73	6	1	19	22	23	18	8	3	4	0.81	0.85	48	52
	Both sexes	312	3	6	16	25	23	16	8	3	6	1.20	0.96	50	50
(a) Trauma without gross hemorrhage	Male	102	1	8	13	25	25	18	8	2	6	0.99	0.95	47	53
	Female	44	4	0	16	21	25	18	11	5	4	2.18	0.00	41	59
	Both sexes	146	2	5	14	24	25	18	9	3	6	2.28	0.85	45	55
(b) Electrocutions, suffocations and drownings	Both sexes	45	2	5	20	29	22	18	2	2	4	3.28	0.80	56	44
(c) Poisoning by carbon monoxide, hydrocyanic acid, etc.	Both sexes	73	7	12	22	29	15	10	4	1	4	13.74	0.003	70	30
(d) Poisoning by alcohol	Both sexes	48	0	2	12	19	29	17	17	4	4	6.17	0.11	33	67

Every pathologist is familiar with the case in which an obviously ill patient dies but no cause of death can be found. Moreover, in this series the coroner's records are apt to be incomplete concerning symptoms previous to injury.

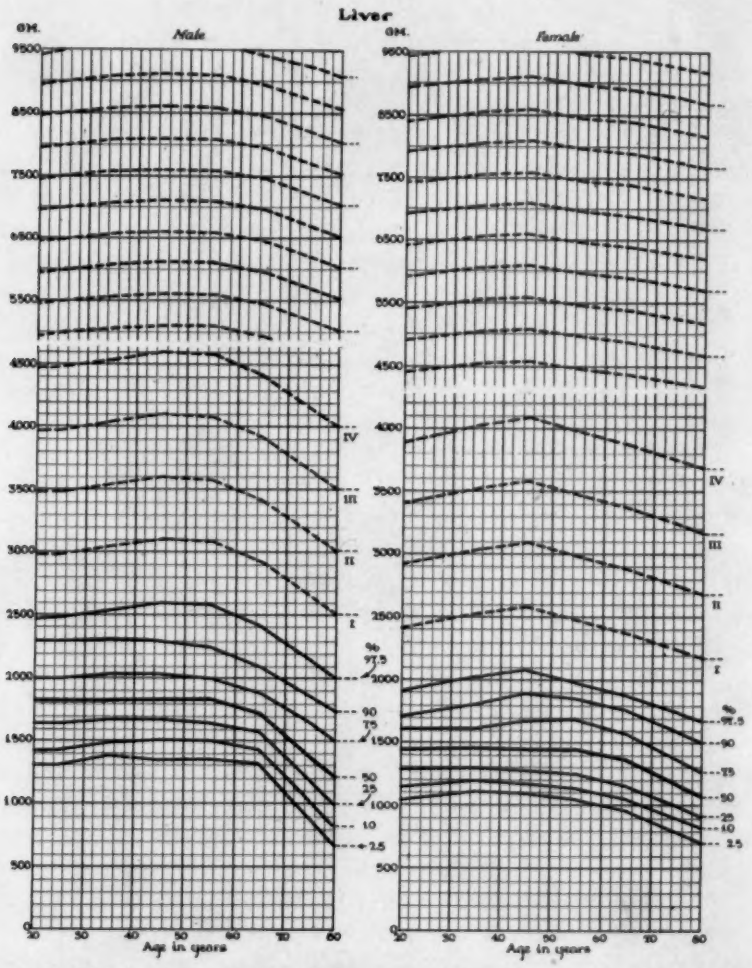

Chart 7.—Work chart of 500 Gm. zones of hypertrophy of the weight of the liver of both the male and the female superimposed above the 97.5 percentile lines of chart 3. Above zone IV the scale was reduced in order to include a sufficient number of zones for pathologic weights.

Zones of Hypertrophy.—In order to make the standards of normal variability useful for Dr. Barron's purposes, namely, degree of hypertrophy of the liver and the spleen in various disease conditions, zones of 500 Gm. for the liver and 100 Gm. for the spleen were drawn in above the 97.5 percentile line, as shown in charts 7 and 8. Inspection

of chart 3 or 7 indicates that the estimate of the upper limit of the normal weight of the liver at 2,200 Gm. made by Barron and Litman [1] would have included approximately from 10 to 15 per cent of the livers of normal males, and especially those of men under 60 years of age,

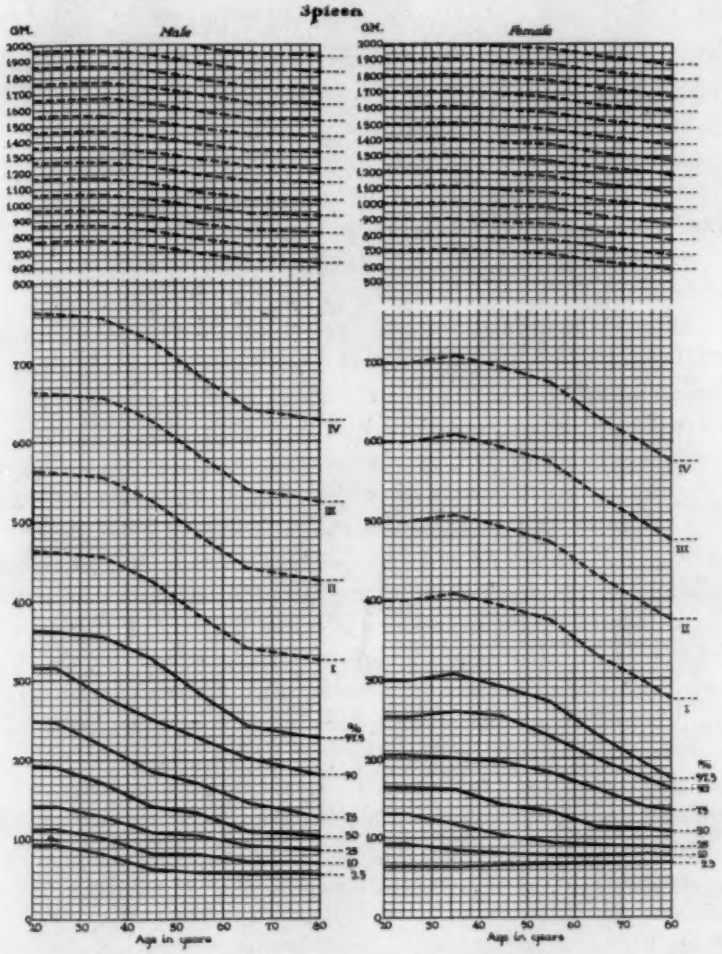

Chart 8.—Work chart of 100 Gm. zones of hypertrophy of the weight of the liver of both the male and the female superimposed above the 97.5 percentile lines of chart 4. Above zone IV the scale was reduced in order to include a sufficient number of zones for pathologic weights.

while certain hypertrophied livers in females would not have been considered enlarged. Inspection of charts 4 and 8 shows that their estimate of 300 Gm. for the upper limit of the normal weight of the spleen would include as hypertrophied about 10 per cent of the spleens in

normal young men and a few of those of young women, while after middle age certain hypertrophied organs would not have been included in their series. This would indicate, on the basis of their assumption that spleens weighing 300 Gm. and livers weighing 2,200 Gm. are palpable, that about 15 per cent of the livers of healthy mature men are palpable and about 10 per cent of the spleens of young men are palpable. This fits with the common clinical practice of accepting, in the absence of symptoms, a just palpable liver or spleen as probably normal. Since they were interested primarily in the very large livers and spleens, weighing 4,000 and 550 Gm., respectively, these findings will not affect their analysis of the importance of hepatomegaly and splenomegaly in differential diagnosis.[20]

Comparison of the Data for Accidental Deaths, Which Were Not Used in Establishing the Standard, With the Normal Standard.—The effect of gross hemorrhage on the weight of both organs is shown in charts 9 and 10, in which the weights from the hemorrhagic group, (1) ill less than twenty-four hours, (*A*) no additional disease, (2) trauma with gross hemorrhage, are plotted on the standards. On inspection, a disproportionate number of weights of both organs seems to fall in the lower zones of normal variability, indicating that massive hemorrhage shortly before death materially lowers the weight of both the liver and the spleen. Whether or not this disproportion is due to chance in sampling or to the gross hemorrhage has been tested by Chi-square in the same manner as the standard was tested.

The steps in calculating Chi-square for the weights of the liver in males are illustrated in table 6. The value of P for a given number of zones, n', and the value of Chi-square obtained may be found in Elderton's tables of Chi-square (Pearson),[21] in a nomogram given by Dunn [22] and in Fisher's tables of Chi-square,[23] when n equals $(n' - 1)$. For weights of livers of the male the Chi-square of 354 is so great that such deviations from the expected number in each zone would not occur by chance once in a million times, since P is less than 0.000000.

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20. Dr. Barron will report later on hypertrophy of the liver and spleen as measured by these standards. We hope ultimately to present a compromise by rank correlation of the interrelation between variability of both organs in the same disease conditions.

21. Pearson, Karl: Tables for Statisticians and Biometricians, ed. 2, London, The Biometric Laboratory, University College, 1924, pt. 1.

22. Dunn, H. L.: Physiol. Rev. **9**:275, 1929.

23. Fisher, R. A.: Statistical Methods for Research Workers, ed. 3, London, Oliver & Boyd, 1930.

As stated before, in common statistical practice a P of 0.01,[24] indicating that chance could cause such a difference only once in a hundred times, is considered adequate evidence of a real difference between two samples. Hence the liver of the female and the spleen of both the male and the female in the hemorrhagic group are also significantly different from the standard, because their P's are 0.003, 0.000000 and 0.000000, respectively. Since these differences, as illustrated in charts 9 and 10 and

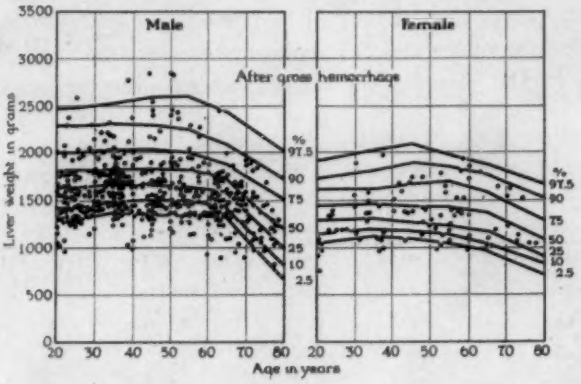

Chart 9.—Graphs showing the weights of the livers from normal males and females dying of trauma with gross hemorrhage plotted on the standards of normal variability of liver weight, chart 3.

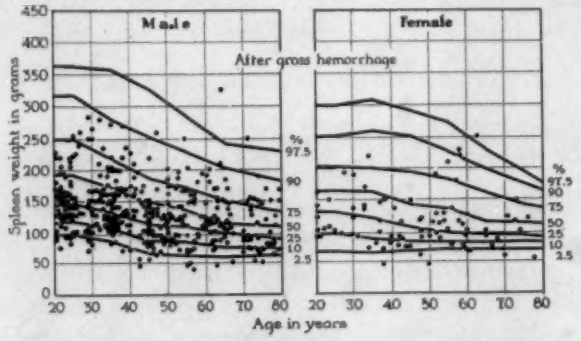

Chart 10.—Graphs showing the weights of the spleen from normal males and females dying of trauma with gross hemorrhage plotted on the standards of normal variability of spleen weight, chart 4.

24. For the convenience of those who do not have the statistical tables at hand, the following table gives the values of Chi-square for a given number of zones, n', at which P is 0.01:

n'	8	6	4	2
χ^2	18	15	11	9

tables 7 and 8, consist of a general lowering of the weights, the interpretation is made that massive hemorrhage materially lowers the weight of both the liver and the spleen.

In like manner, the weights for the other groups excluded from the normal data for accidental deaths listed in table 1 were compared with the standard and the findings summarized in tables 7 and 8. Since fatty degeneration of the liver causes marked hypertrophy, this group for the liver was separated from the groups in which additional disease was present. Also the number of weights in comparable zones of the standards for the males and the females were combined, because no sex differences in the distribution of the weights on the standard were

TABLE 6.—*The Chi-Square Method of Comparing Observed with Theoretically Expected Number of Weights in Each Zone of the Normal Standard*

	Percentile Zones								
Expected	Above 97.5 Line	97.5 to 90 Line	90 to 75 Line	75 to 50 Line	50 to 25 Line	25 to 10 Line	10 to 2.5 Line	Below 2.5 Line	Totals
Expected percentage of weights	2.5	7.5	15	25	25	15	7.5	2.5	100
Expected number of weights, T	10.15	30.45	60.90	101.50	101.50	60.90	30.45	10.15	406
Observed number of weights, O*	5	14	28	53	82	88	77	59	406
T — O	+5.15	+16.45	+32.90	+48.50	+19.50	−27.10	−46.55	−48.85	0
$(T - O)^2$	26.52	270.60	1082.41	2352.25	380.25	734.41	2166.90	2386.32	
$(T - O)^2/T$	2.61	8.89	17.77	23.17	3.75	12.06	71.16	235.11	374.52

χ^2 = sum of $(T - O)^2/T = 374.52$
n′ of Elderton's table of χ^2 = number of zones = 8 ∴ P = 0.000000

* Example: The hemorrhagic group, (1) ill less than twenty-four hours, (A) no additional disease, (2) trauma with gross hemorrhage, weights of 406 livers from males, shown in the first panel of chart 9.

demonstrable for any disease. Whenever the combining of the numbers of the sexes did not increase the number expected in the end-zones to ten, the zones were combined until at least that many were expected, and then Chi-square was calculated for the resulting reduced number of zones, 6, 4 or 2, as indicated by the values of n' in the tables.[24]

Study of the tables indicates that when disease was present at time of injury, the variability was usually significantly incerased, i. e., a disproportionate number fell in the extreme upper and lower zones, and when illness had lasted more than one day, an increased number of weights of livers fell in the lower ranges, but the weights of spleens showed no significant deviation from the normal. The latter findings are in agreement with Jackson's summary [8] of the effects of inanition on both the liver and the spleen, namely, that both are reduced, but the reduction of the spleen cannot be demonstrated as early in inanition as

TABLE 7.—*Comparison of the Weights of the Liver From the Accidental Deaths, Not Used in Establishing the Standard, With the Normal Standard*

	Number of Weights for Both Sexes	Percentage of Weights											Percentage of Weights	
		Above 97.5 Line	Between the Percentile Lines: 97.5 to 90	90 to 75	75 to 50	50 to 25	25 to 10	10 to 2.5	Below 2.5 Line	n′	χ^2	P	Above 50 Line	Below 50 Line
Percentage of weights expected		2.5	7.5	15	25	25	15	7.5	2.5				50	50
(1) Accidents Without Gross Hemorrhage														
(I) Ill less than 24 hours:														
(B) Additional disease	97	9	11	11	23	20	15	5	6	6	11.32	0.05	54	46
(C) Fatty liver	65	26	12	28	20	8	4	0	2	4	61.70	0.00	86	14
(II) Ill 1 day or more:														
(A) No additional disease	175	2	6	13	22	22	19	9	7	6	11.95	0.04	43	57
(B) Additional disease	130	9	14	14	14	20	14	10	5	6	32.90	0.00	51	49
(C) Fatty liver	57	25	31	12	14	11	7	0	0	4	57.88	0.00	82	18
(2) Trauma With Gross Hemorrhage														
(I) Ill less than 24 hours:														
(A) No additional disease	489	1	4	8	13	22	20	17	15	6	302.51	0.00	26	74
(B) Additional disease	47	4	5	4	13	19	19	21	15	4	23.55	0.00	26	74
(C) Fatty liver	23	13	9	17	22	26	0	4	9	2	1.08	0.30	61	39
(II) Ill 1 day or more:														
(A) No additional disease	92	2	2	12	22	20	17	11	14	6	26.03	0.00	38	62
(B) Additional disease	25	0	0	12	36	8	32	8	4	2	0.04	0.80	48	52
(C) Fatty liver	9	..	..	..	..	..	..	..	..	..	....	....	78	22
(3) Poisoning with Heavy Metals														
(I) Ill less than 24 hours:														
(A) No additional disease	23	0	4	13	9	26	35	9	4	2	2.13	0.15	26	74
(B) Additional disease	15	0	0	20	13	20	20	13	14	..	....	....	33	67
(C) Fatty liver	3	..	..	..	..	..	..	..	..	..	....	....	..	..
(II) Ill 1 day or more:														
(A) No additional disease	14	0	21	22	14	14	22	7	0	..	....	....	57	43
(B) Additional disease	6	..	..	..	..	..	..	..	..	..	....	....	..	..

TABLE 8.—*Comparison of the Weights of the Spleen From the Accidental Deaths, Not Used in Establishing the Standard, With the Normal Standard*

	Number of Weights for Both Sexes	Percentage of Weights											Percentage of Weights	
		Above 97.5 Line	Between the Percentile Lines: 97.5 to 90	90 to 75	75 to 50	50 to 25	25 to 10	10 to 2.5	Below 2.5 Line	n′	χ^2	P	Above 50 Line	Below 50 Line
Percentage of weights expected		2.5	7.5	15	25	25	15	7.5	2.5				50	50
(1) Accidents Without Gross Hemorrhage														
(I) Ill less than 24 hours:														
(B) Additional disease	162	7	8	13	18	22	16	7	9	6	14.00	0.02	46	54
(II) Ill 1 day or more:														
(A) No additional disease	175	3	8	12	24	26	13	8	6	6	4.33	0.55	47	53
(B) Additional disease	187	10	9	19	17	21	12	9	3	6	22.84	0.00	55	45
(2) Trauma With Gross Hemorrhage														
(I) Ill less than 24 hours:														
(A) No additional disease	489	1	1	11	16	29	23	13	6	6	112.49	0.00	29	71
(B) Additional disease	70	5	6	9	14	30	16	10	10	4	7.83	0.05	34	66
(II) Ill 1 day or more:														
(A) No additional disease	92	3	5	17	19	23	23	7	3	4	6.01	0.11	44	56
(B) Additional disease	34	3	9	6	17	32	21	9	3	2	2.94	0.10	35	65
(3) Poisoning with Heavy Metals														
(I) Ill less than 24 hours:														
(A) No additional disease	23	0	4	17	18	22	35	4	0	2	1.08	0.30	39	61
(B) Additional disease	18	0	6	22	22	22	22	6	0	..	....	....	50	50
(II) Ill 1 day or more:														
(A) No additional disease	14	7	7	7	29	36	7	7	0	..	....	....	50	50
(B) Additional disease	6	..	..	..	..	..	..	..	..	..	....	....	..	..

can the reduction of the liver. They also indicate why the older standards are lower than those presented here, and the age changes are different, even when care was taken to exclude all directly diseased organs (Greenwood,[3] Greenwood and Brown,[4] Bean and Baker,[5] and Bean [6]).

COMMENT

The chief value of the charts presented here as standards of the normal weight of the liver and the spleen, over and above the means with their standard errors for age periods, is that they make it possible to compare a small series of cases from both sexes and covering the total adult age range without any subdivision of the data. In many disease conditions a series of 50 cases is large. If this group has to be divided into two sex groups, then into two or three age groups, the various groups become too small for reliable statistical comparison of the means. Moreover, the weights for a given disease can be plotted on the standards, as the data are gradually collected and an impression of the age and sex trend of the weight of the liver and the spleen in that disease gained before sufficient data are collected to justify the tedious calculations of means and standard deviations.

In using these charts it should be remembered that associated massive hemorrhage will lower the weights; that in wasting diseases most organs are reduced in weight; that if death in a given disease usually occurs with the spleen dilated, the weights will tend to fall in the upper zones, and conversely, if death consistently occurs with the spleen contracted, the weights will tend to fall in the lower zones; that while the 97.5 percentile line may be considered an approximation of the upper limit of normal variability, two to three weights in every hundred of weights in normal subjects, as can be judged by ordinary pathologic diagnosis, will be expected to fall above this line, and that the standards for females are not highly reliable, owing to the small number of cases.

SUMMARY

1. Graphic standards of the normal variability in the weight of both the liver and the spleen for both sexes for the age period from 20 to 80 years have been presented. These standards were constructed from the weights of livers and spleens from persons dying within twenty-four hours of injury, of trauma without any associated gross hemorrhage, of suffocation, of drowning, of electrocution or of poisonings by such substances as carbon monoxide, narcotics, hydrocyanic acid, strychnine and alcohol, and having no history of illness or any disease demonstrable at necropsy except moderate arteriosclerosis and such evidence of old healed infections as pleural adhesions.

2. When compared with these standards, the weights of both the liver and the spleen were materially reduced in persons dying of trauma accompanied by massive hemorrhage.

3. From these charts the deviation of the weights of the liver or the spleen in a given disease condition from the normal range of weights may be determined by plotting the weights on these standards and testing for the significance of the deviation of the observed from the expected number by the Chi-square method.

4. To these standards of normal variability in weight there have been added for the liver 500 Gm. zones of degrees of hypertrophy, and for the spleen, 100 Gm. zones.[25]

25. Photolithic reproductions of charts 7 and 8, such as are being used in Dr. Barron's study, can be obtained at cost (approximately $5 for 200 charts) by writing to the author. If preferred, similar charts may be constructed on any desired scale from tables 2 and 3.

NEGATIVE RESULT FROM TRANSFER OF MATERIAL FROM HUMAN ACUTE MULTIPLE SCLEROSIS TO MACACUS RHESUS UNDER OPTIMUM CONDITIONS

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The etiology of the large group of human diseases associated with disseminated foci of demyelinization attacking mostly the white matter of the central nervous system is, as yet, unknown. Neuropathologic studies have served to differentiate certain types which, however, do not fall into clearcut clinical categories. Such studies also reveal that the tissue reactions in the several types are compatible with the inflammatory states called forth by infectious agents, and suggest that multiple sclerosis, Schilder's disease, disseminated encephalomyelitis and vaccinal encephalitis should be assumed to be of infectious origin and studied accordingly. Pathologic research has not shown them to be noninfectious.[1]

Material from persons with any type of encephalitis is rarely obtained in the fresh state, unformaldehydized. Optimum conditions for culture or for experiments in the transmission of the disease to monkeys include the availability of fresh brain from a subject with an acute and rapidly progressing disease, aseptically removed a short time after death. When such conditions are met, we believe the results, although negative, are important for record. We present this case from nine others of a similar negative nature because of the uniquely favorable situation for study.

REPORT OF CASE

H. K., a woman, aged 22, entered the University of Chicago Clinics on April 26, 1932, complaining of periodic attacks of headache, dizziness and vomiting occurring once or twice a year for five or six years. During the last month there appeared staggering to the left, diplopia, transient and recurrent left-sided numbness, weakness of the right side of the face and jaw, and twitching of the right leg. Lying on the right side produced dizziness and nausea; on the left side, tinnitus in the left ear.

The investigation was carried on with the aid of a grant from the Josiah Macy Jr. Foundation.

From the Department of Hygiene and Bacteriology and the Division of Neurology and Neurosurgery of the University of Chicago.

1. Grinker, R. R., and Bassoe, P.: Disseminated Encephalomyelitis and Its Relation to Other Infections of the Central Nervous System, Arch. Neurol. & Psychiat. **25**:723 (April) 1931.

Physical examination showed anisocoria, coarse horizontal nystagmus to the right and fine, rapid nystagmus to the left and up. Diplopia was produced by a weak right external rectus muscle. The jaw deviated to the left, and the left side of the face had a reduction in all sensory modalities. Hearing was diminished in the left ear, and there was peripheral facial weakness on the left side. Terminal action tremor and adiadokokinesis developed in the left arm, and in that extremity all sensory qualities were diminished. The flexors of both legs were weak; on the left, tone was increased and an action tremor was present. The lower deep reflexes were exaggerated, and a bilateral positive Babinski sign and patellar and ankle clonus were elicited.

The disease progressed rapidly with an increase in severity of all the signs and symptoms. In addition, retention of urine developed, the left arm became spastic and then a quadriplegia developed. Vomiting, difficulty in speaking and swallowing, and increasing lethargy indicated a bulbar and encephalitic extension. The patient died on May 26, with terminal bronchopneumonia and urinary infection.

The Wassermann reactions of the blood and spinal fluid were negative. The pressure of the cerebrospinal fluid was normal, and there were 10 lymphocytes per cubic millimeter. The protein content was only 47 mg. per hundred cubic centimeters. The benzoin curve showed a rise in the middle zone. The leukocyte count for the blood was only 7,600 per cubic millimeter.

Necropsy.—Evidences of a moderately severe infection of the urinary tract were found. There was bilateral bronchopneumonia, which was the cause of death. The brain and the spinal cord were removed within one hour after death. There was an excess of cerebrospinal fluid in the basal cisterns. The surfaces of the brain were flattened and edematous. The vessels of the leptomeninx and of the external and internal surfaces of the brain were extremely engorged with blood.

Histologic Examination.—Numerous blocks from the brain, brain stem and spinal cord were examined, the special staining methods being used to demonstrate myelin sheaths, fat, nerve fibers, cells and connective tissue.

The essential lesions were distributed irregularly throughout the central nervous system, including the brain and the brain stem, but were more numerous in the medulla and in the spinal cord. They were sharply limited to the white matter, not extending to the central gray matter or to the gray cortex. Myelin sheath stains showed them to be rather sharply outlined areas of complete demyelinization. Scarlet r brought out the products of degeneration of myelin in the form of simple globules of fat, free in the tissue, included in the numerous proliferated microglia cells and within the intra-adventitial vascular spaces. The nerve fibers themselves were less severely affected, but within the areas of demyelinization they were swollen and tortuous and many were fragmented. The glia were proliferated near the loci, and the ganglion cells nearby showed marked degenerative changes. Many of the blood vessels in the damaged areas were infiltrated with lymphocytes and an occasional plasma cell and polymorphonuclear leukocyte. The perivascular connective tissue was increased.

TRANSMISSION AND CULTURE EXPERIMENTS

Pieces of nerve tissue were taken aseptically from the cortex, pons and spinal cord and separately ground in covered sterile mortars with 3 cc. of sterile broth. Intracerebral injections of the indivi lual specimens were made into three monkeys and of pooled material into a fourth monkey. One rabbit and three guinea-pigs were given injections of

the pooled specimen, the rabbit intracerebrally and the guinea-pigs intraperitoneally and subcutaneously. The rabbit and guinea-pigs were discarded after a month's observation, during which there was no abnormal temperature, local lesion or abnormal behavior. The temperature of the monkeys was recorded daily for over a month without significant variation from normal. They were killed by inhalation of ether ten months after inoculation; meanwhile they appeared normal in every respect. The brains and spinal cords were placed immediately in a diluted solution of formaldehyde, U. S. P. (1:10). Blocks were removed from various loci and cut and stained to demonstrate cells, myelin sheaths and fat. Grossly and histologically, there was not the slightest deviation from normal.

Bacteriologic examinations were made of the individual specimens. By means of Pasteur pipets, tissue emulsions were added to an assortment of special and routine mediums incubated under a variety of conditions. Extreme precautions were taken in the technic, and all materials were controlled for sterility. A green-producing streptococcus was grown from the cortical tissue, a pleomorphic streptococcus from the pons and Staphylococcus albus from the three sources. While it must be remembered that this patient died of bronchopneumonia, these bacteriologic findings cannot be attributed solely to an antemortem or even an agonal systemic infection. Our experience in the bacteriologic study of the group of cases of encephalitis and of a series of twelve controls of fresh material from the brain of patients dying of somatic diseases leads us to think that it was almost impossible to avoid occasional contamination by bacteria from the air. We base this opinion on the numbers and kinds of bacteria grown on blood agar plates exposed to the air in the small room in which the bacteriologic work was done. Specifically, we have isolated from the air the same bacteria that were grown from the brain and spinal cord in this case. For these reasons we attach no significance, as regards the cerebral condition, to our bacteriologic findings.

CONCLUSION

Material from the brain and spinal cord in an acute and rapidly fatal case of multiple sclerosis cultured and inoculated intracerebrally into monkeys gave entirely negative results.

Laboratory Methods and Technical Notes

A RAPID METHOD FOR THE DEMONSTRATION OF RETICULUM AND COLLAGEN FIBERS IN FROZEN SECTIONS

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A number of methods have been devised for the demonstration of reticulum fibers in tissue sections by silver impregnation. The method of Bielschowsky [1] was useful but time-consuming. In 1921, Perdrau [2] published a modification of Bielschowsky's technic which cut the time required in half, i. e., from about eight days to four. Frozen sections were used in both methods. More recently, Foot [3] published a rapid method requiring the use of paraffin sections of tissue fixed in Zenker's solution. His method consumes about an hour's time after the sections are fixed to the slides.

In the method to be described the time required is about an hour and a half after the frozen sections have been cut. The advantages of this method consist not only in the ease and rapidity with which the technic can be carried out, but also in the sharp differentiation which results between the reticulum fibers and the collagen fibers. The reticulum becomes jet black and appears very sharp, while the coarse collagen fibers are deep brown. This results in a colorful picture which does not require counterstaining to demonstrate the connective tissue, although counterstaining can be done, as, for example, with van Gieson's solution.

1. Fix the tissue in a diluted solution of formaldehyde, U. S. P. (1:10) in the usual manner.

2. Cut the frozen sections from 5 to 10 microns thick.

3. Wash the sections in three changes of distilled water.

4. Place them in a 10 per cent solution of ammonium hydroxide heated at 60 C. for fifteen minutes. The bottom shelf of the paraffin oven is a good place for the small Stender dishes used.

5. Wash the sections in three changes of distilled water.

6. Place them in a 0.3 per cent solution of potassium permanganate for five minutes.

7. Wash them in distilled water for a few seconds.

8. Decolorize them in a 1.5 per cent solution of oxalic acid until all the brown color has disappeared. Sections should not be left in this solution longer than necessary. Each section should be treated separately.

9. Wash them thoroughly in four or five changes of distilled water.

10. Place them in a 5 per cent solution of silver nitrate kept at 60 C. in the paraffin oven for one hour.

1. Bielschowsky, Max: Anat. Anz. **36**:401, 1910.
2. Perdrau, J. R.: J. Path. & Bact. **24**:117, 1921.
3. Foot, N. C.: J. Tech. Methods **12**:117, 1929.

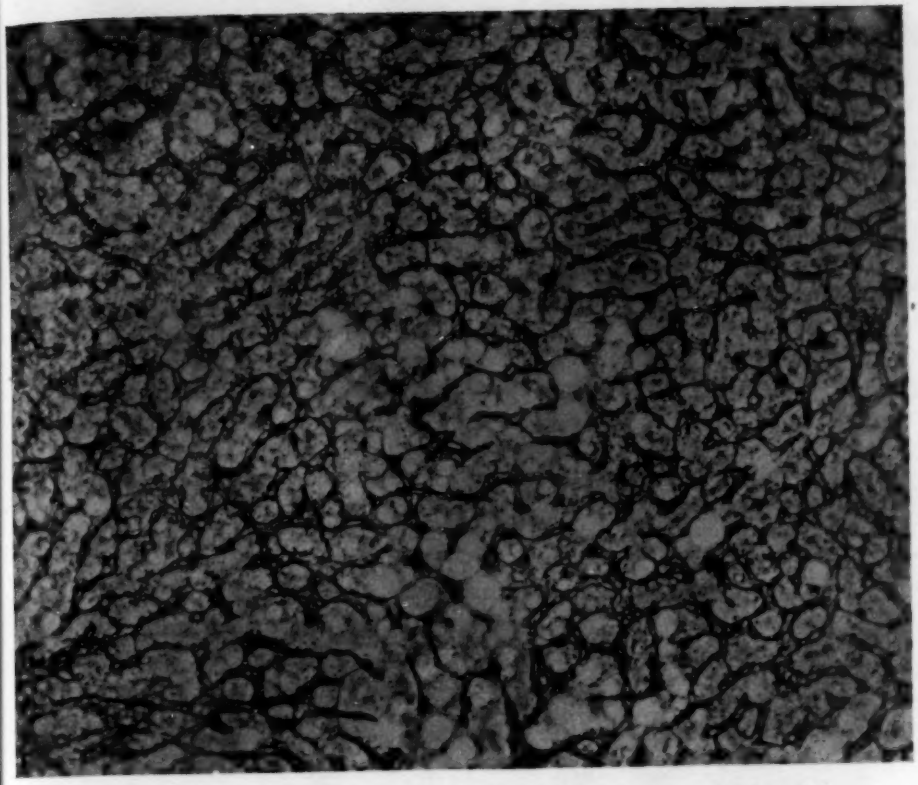

Fig. 1.—Human liver showing fine reticulum with reticulum stain; × 300.

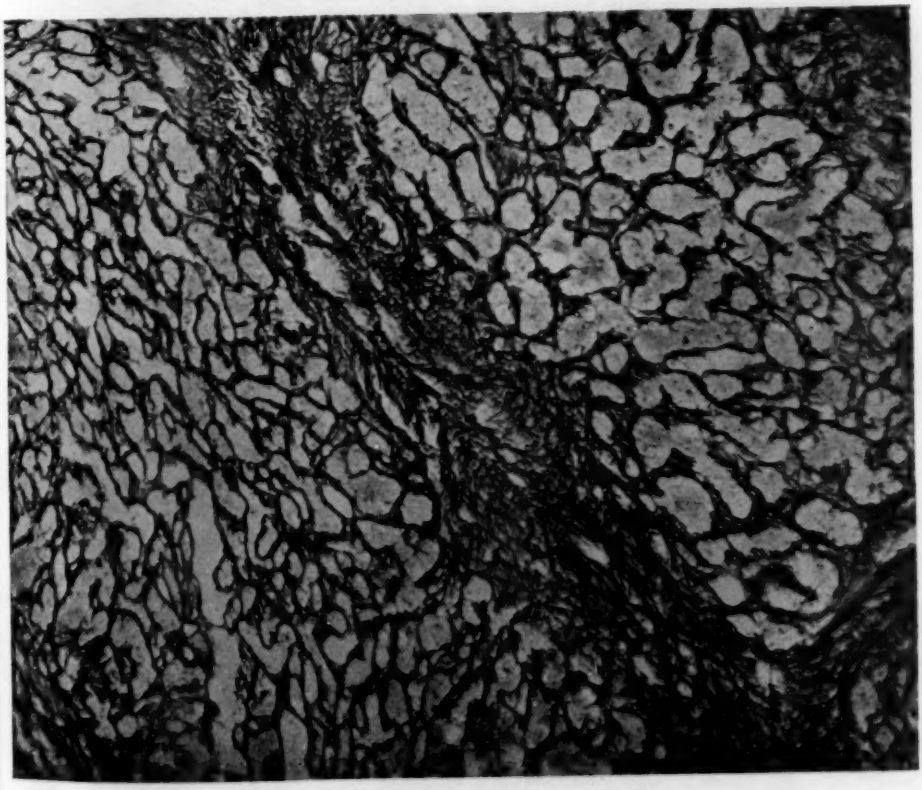

Fig. 2.—Cirrhosis of the human liver; × 300.

11. Wash them in two changes of distilled water.

12. Place the sections in a solution of ammoniacal silver nitrate heated at 60 C. for fifteen minutes. The ammoniacal silver solution is prepared as follows:

Take 8 cc. of 10 per cent solution of silver nitrate. Add 6 drops of 10 per cent solution of sodium hydroxide. A brownish-black precipitate forms. Make up a fresh 10 per cent solution of ammonium hydroxide. Add this to the precipitated silver solution drop by drop until it is almost entirely cleared. Only a few small particles of the brownish-black precipitate should be allowed to remain. Then dilute it up to 28 cc. with distilled water. The resulting solution constitutes the ammoniacal silver.

13. Wash the sections quickly in three changes of distilled water.

14. Place them in a 30 per cent solution of formaldehyde (30 cc. of 40 per cent solution of formaldehyde plus 70 cc. of distilled water) heated at 60 C. from one to three minutes.

15. Wash the sections in a large basin of tap water and snatch onto slide.

16. Cover the section with a few drops of absolute alcohol, and blot into position.

17. Complete the dehydration with two changes of absolute alcohol, blot, clear in equal parts of aniline oil and xylene for three minutes, wash in xylene and mount in gum damar or neutral Canada balsam.

If photomicrographs are desired, it is better to subject the section after step 14 to a toning process in a solution of gold chloride as follows:

1. Place the sections in a solution of gold chloride in distilled water 1:300 for from three to five minutes.

2. Wash them in distilled water and place in a 5 per cent solution of sodium hyposulphite (thiosulphate) from three to five minutes.

3. Then proceed with step 15.

This removes the brownish tint of the collagen fibers and cellular structures, leaving the collagen fibers a dull reddish purple.

SUMMARY

A rapid method for the demonstration of reticulum and collagen fibers in frozen sections is described. It has advantages over Perdrau's method in that (*a*) it is more rapid and (*b*) the collagen fibers appear dark brown, thus affording a colorful picture not requiring the use of a counterstain. If desired for photographic purposes, sharper contrast can be secured by a toning process.

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General Review

RELATION OF THE SUPRARENAL GLANDS TO RESISTANCE

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CONTENTS

I. Relation of the Suprarenal Glands to the Formation of Antibodies.
II. Relation of the Suprarenal Glands to Anaphylaxis.
III. Relation of the Suprarenal Glands to Natural and Acquired Resistance.
IV. The Cortical Hormone and Natural Resistance.
V. Significance of the Depression in Natural Resistance Following Suprarenalectomy.

There is a great deal of evidence both from morphologic and from physiologic studies that the suprarenal glands play a significant rôle in the defensive mechanism of the body, particularly against intoxications and infectious diseases. The active participation of the suprarenal cortex in this process has long been suspected by pathologists. Hyperemia, edema, hemorrhage and focal necrosis occur in the suprarenal glands in cases of burns of the skin, food poisoning and acute infections.

The suprarenal glands of guinea-pigs poisoned with diphtheria toxin or arsenicals are severely injured (Roux and Yersin [1]). In a study of 2,800 guinea-pigs killed by injections of diphtheria toxin, Rosenau and Anderson [2] were able to confirm these observations.[3] Distemper in cats

From the Laboratory Division, Montefiore Hospital, and the Department of Pathology, School of Medicine, Cornell University.

1. Roux, E., and Yersin, A.: Ann. Inst. Pasteur **3**:273, 1889.

2. Rosenau, M. J., and Anderson, J. F.: A Stomach Lesion in Guinea Pigs Caused by Diphtheria Toxin and Its Bearing upon Experimental Gastric Ulcer, U. S. Hyg. Lab. Bull. no. 22, 1906.

3. Gastric ulcers and erosions were present in almost two thirds of these pigs (Marine, David: Some Effects of Suprarenal Injury on Natural and Acquired Resistance, in Contributions to the Medical Sciences in Honor of Dr. Emanuel Libman by His Pupils, Friends and Colleagues, New York, International Press, 1932). Rosenau and Anderson [2] could not have known that similar ulcers regularly occur following removal or severe injury of the suprarenals in the dog, cat, rabbit, guinea-pig and rat. Marine expressed the belief, based on experimental observations, that the ulcers seen in severe burns and in diphtheria poisoning are associated with the severe suprarenal cortical injury occurring in such conditions.

is associated with injury to the suprarenal cortex. Marine [4] observed that the lesions begin as focal necrosis of the cells of the reticular and fascicular layers but as a rule do not extend to the glomerular zone. With recovery, calcification of the necrotic areas occurs in a large percentage of cats. Calcification was observed in the cortex in 25 per cent of a series of 257 cats. In influenza and in peritonitis, focal necrosis of the cortex occurs. Influenzal asthenia may be associated with suprarenal injury. The amount of cholesterol and its esters in the cortex is greatly decreased during acute infectious diseases.[5] These observations led to the view that the suprarenal cortex is concerned directly or indirectly with the neutralization of toxins. It was noted that patients suffering from Addison's disease succumb readily to drugs and toxins in amounts generally innocuous to a normal person.

Status lymphaticus, since the work of Wiesel,[6] Hedinger,[7] Paltauf [8] and others, has been shown to have some important relation to the suprarenal glands. The marked hyperplasia of the thymus and of the lymphoid tissue following experimental suprarenal insufficiency in rats and cats was first pointed out by Jaffe,[9] and the similarity of this experimental condition to human status thymicolymphaticus was emphasized by these investigators. Status lymphaticus is particularly associated with the cortex. Both in status lymphaticus and in experimental suprarenal insufficiency there are lowered resistance to poisons and marked changes in temperature.[10]

I. RELATION OF THE SUPRARENAL GLANDS TO THE FORMATION OF ANTIBODIES

Experiments dealing with the antibody-forming capacity of animals following bilateral suprarenalectomy have been limited because of technical difficulties. Immunologic studies bearing on this subject may be divided into two groups: (1) those on the effect of injections of epinephrine into the normal animal on the complement titer and on the formation of antibodies, and (2) those on the influence of partial or complete suprarenalectomy on the formation of antibodies.

Josué and Paillard [11] studied the opsonic properties of rabbits' blood after the intravenous injection of epinephrine and found that

4. Marine, David: J. Exper. Med. **43**:495, 1926.
5. Aschoff, L.: Lectures on Pathology, New York, Paul B. Hoeber, Inc., 1924, p. 101.
6. Wiesel, J.: Internat. Clin. **2**:288, 1905.
7. Hedinger, E.: Frankfurt. Ztschr. f. Path. **1**:527, 1907.
8. Paltauf, R.: Wien. klin. Wchnschr. **2**:877, 1889; **3**:172, 1890.
9. Jaffe, H. L.: J. Exper. Med. **40**:325, 619 and 753, 1924.
10. Marine, David: Arch. Path. **5**:661, 1928.
11. Josué, O., and Paillard, H.: Compt. rend. Soc. de biol. **68**:657, 1910.

this drug was without effect. The production of sheep cell hemolysins and of typhoid agglutinins in rabbits following the subcutaneous and intravenous administration of epinephrine was studied by Bijlsma [12] and Hrma.[13] No appreciable effect was obtained. Bijlsma [12] observed also that unilateral suprarenalectomy in rabbits was without influence on the production of hemolysins and agglutinins. A decrease in the complement titer of the serum of guinea-pigs after the administration of epinephrine and atropine was reported by Pinner.[14] Ecker and Rogoff [15] found no change in the complement titer of the blood of rabbits which survived double suprarenalectomy. The observations of Ecker and Rogoff were confirmed by Také and Marine [16] in suprarenalectomized rabbits. Hektoen and Curtis [17] removed the suprarenal glands from normal dogs and from dogs in which the antibody curve was at its height and found that no change in the curve followed. Gates [18] studied the formation of hemolysins and agglutinins in guinea-pigs and in 3 rabbits after the removal of from three fourths to seven eighths of the suprarenal glands. He observed no noteworthy effects. Také and Marine [16] found that rabbits which have survived removal of both suprarenal glands have higher hemolysin titers than normal rabbits. The highest titer in a series of 30 normal rabbits was 1,500, or the same as the lowest titer in 14 suprarenalectomized rabbits. The average titer for the suprarenalectomized rabbits was more than twice that for the normal animals. Také and Marine could find no explanation of the increase in the formation of hemolysins, but they expressed the belief that it is associated with a loss of the cortex rather than of the medulla. They suggested that the disturbance in the formation of antibodies is due to a loss of some regulatory and inhibitory influence which the cortex normally exerts on the irritability and susceptibility of the cells of the body. In subsequent experiments Jaffe and Marine [19] studied the effect of suprarenalectomy on the formation of agglutinins in rats.

The studies included 30 bilaterally suprarenalectomized and 3 unilaterally suprarenalectomized rats, 4 animals in which the perisuprarenal tissue was traumatized and 31 controls. The rats that had been operated on were repeatedly inoculated with typhoid vaccine in amounts of 0.2 cc. between eight and forty days after suprarenalectomy. Three or four injections were given at three day intervals. Titrations were made every third or fourth day after the last injection.

12. Bijlsma, U. G.: Centralbl. f. Bakt. (Abt. 1) **86**:246, 1921.
13. Hrma, A.: Casop. lék. cesk. **61**:1217, 1922.
14. Pinner, M.: Beitr. z. klin. d. Tuberk. **46**:471, 1920.
15. Ecker, E. E., and Rogoff, J. M.: J. Immunol. **6**:355, 1921.
16. Také, N. M., and Marine, David: J. Infect. Dis. **33**:217, 1923.
17. Hektoen, L., and Curtis, A. R.: J. Infect. Dis. **17**:409, 1915.
18. Gates, F. L.: J. Exper. Med. **27**:725, 1918.
19. Jaffe, H. L., and Marine, David: J. Infect. Dis. **35**:334, 1924.

It was found that rats immunized with typhoid vaccine within three weeks following bilateral suprarenalectomy had agglutinin titers averaging from two to three times greater than those of the controls. Six weeks after suprarenalectomy no difference in the formation of agglutinins could be determined between normal animals and suprarenalectomized rats surviving the operation in good condition, although the resistance of the latter to large doses of vaccine was still below normal. These findings were at variance with those of Khorazo, who observed no essential difference in the formation of agglutinins between normal and suprarenalectomized rats.[19] Marine found that suprarenalectomized rabbits form antitoxin to diphtheria toxin as rapidly as or more rapidly than the controls. The antitoxin formation was determined by repeated Schick tests.

The formation of antibodies in suprarenalectomized rats was studied by Perla and Marmorston-Gottesman in a series of experiments.[20]

In preliminary studies on the formation of hemolysins in normal rats[20a] it was found that high titers were obtained following a single intraperitoneal injection of a small amount of sheep cells (1 cc. of a 10 per cent suspension). This rapid method of immunization is definitely advantageous in studying the formation of antibodies in the early period after bilateral suprarenalectomy.[20b] The titer was determined five, eight, eleven and fourteen days after the injection. It was found that the antibody titer varied with the quantity of antigen injected, and the antigen-antibody curve for normal rats was first determined.

In the first group of experiments we determined the influence on the titer of varying the time between suprarenalectomy and the injection of antigen, keeping the amount of antigen injected constant. In the second group of experiments the quantity of antigen injected was varied, but the time after suprarenalectomy was kept constant. In about 70 per cent of the rats the titer was above 1:2,000, and the average titer for 43 normal rats was 1:5,600.[20c] In a large series of suprarenalectomized rats, a study was made of the formation of hemolysins in response to a fixed amount of sheep cells (1 cc. of a 10 per cent suspension) injected intraperitoneally forty-eight hours and seven, fourteen and twenty-eight days after operation. The formation of hemolysins was studied in suprarenalectomized rats which two weeks following the operation were given injections of one-twentieth and of ten times this amount. The formation of hemolysins was studied in rats which were traumatized by tearing the perisuprarenal tissue and two weeks after the operation were given an injection of 1 cc. of a 10 per cent suspension of sheep cells, and the results were compared with those in the normal control rats. The effect of the operative procedure was controlled by removing one kidney in a series of rats and determining the antibody response to sheep cells.

Bilateral suprarenalectomy in rats which subsequently were given intraperitoneally 1 cc. of a 10 per cent suspension of sheep cells resulted in a depression of the hemolysin titer during five weeks following the

20. (*a*) Marmorston-Gottesman, J., and Perla, David: J. Exper. Med. **47**:713, 1928; (*b*) **47**:723, 1928; (*c*) **48**:225, 1928; (*d*) **50**:87, 1929; (*e*) **50**:93 1929.

operation, the depression being most marked during the second week. When 1 cc. of undiluted sheep cells was injected intraperitoneally two weeks after the operation, bilaterally suprarenalectomized rats gave hemolysin titers higher than those of normal rats. The quantity of antigen necessary to yield the maximum titer in suprarenalectomized rats two weeks after operation is ten times the quantity necessary to yield the same titer in normal rats. Traumatization of the perisuprarenal tissue in rats resulted in a decrease in the formation of hemolysins which was even more prolonged than in a corresponding series of suprarenalectomized rats. Traumatization of the perisuprarenal area probably results in severing or injuring the sympathetic or parasympathetic nerves innervating the suprarenals. This injury may cause a depression of the function of the cortex as well as of the medulla.

Though it is well known (Dreyer,[21] Tscheboksaroff [22] and Stewart and Rogoff [23]) that the output of epinephrine from the suprarenal glands is controlled by a nervous mechanism, and that interruption of the nerve pathway results in a diminution of the output, the extent of the nervous control of the function of the cortex is undetermined. Depression of the antibody-forming capacity to small amounts of antigen may be an expression of impaired suprarenal function. However, with the removal of the suprarenal glands in rats, regeneration of thymic and lymphoid tissue occurs.[9] This hyperplasia does not occur following traumatization of perisuprarenal tissue. This lymphoid hyperplasia may be in some way responsible in suprarenalectomized rats for the partial recovery of the antibody-forming capacity several weeks after operation.

Though injections of epinephrine [20d] raise the antibody-forming capacity in suprarenalectomized rats, the diluting fluid, isotonic solution of sodium chloride, was found to have a similar effect. Experiments on a large series of rats demonstrated that repeated injections of large amounts of an isotonic solution of sodium chloride or of sodium acetate restore the antibody titer of suprarenalectomized animals to normal.[20e] The effect of these solutions is not due to diuresis alone, since isotonic dextrose solution does not affect the titer, or to the sodium ion alone, since hypertonic solutions of sodium chloride in small volume have little influence on the titer. It would seem from these observations that both the fluid and the sodium ion are necessary to bring about a restoration of the antibody-forming capacity of suprarenalectomized rats to normal.

These results are in accord with those of Marine and Baumann,[24] who found that the administration of Ringer's solution and of isotonic solutions of sodium chloride and sodium acetate increased the duration

21. Dreyer, G. P.: Am. J. Physiol. **2**:203, 1899.
22. Tscheboksaroff, M.: Arch. f. d. ges. Physiol. **137**:59, 1911.
23. Stewart, G. N., and Rogoff, J. M.: J. Exper. Med. **26**:613, 1917.
24. Marine, David, and Baumann, E. J.: Am. J. Physiol. **81**:86, 1927.

of life of suprarenalectomized cats threefold. Isotonic solutions of dextrose and of glycerin had only a slight life-prolonging effect.

It is well known that the sodium ion plays an important rôle in the water exchange in the tissues. Suprarenalectomy results in a profound disturbance of the water balance. Following removal of the glands, there are a loss of fluid through the intestines, a diminution of the sodium content of the blood (Baumann and Kurland [25]) and an impairment of renal function. These factors result in dehydration of tissues and in a disturbance of the normal cellular physiologic activity. It is possible that the elements in the tissues concerned with antibody formation respond to a lesser degree in the production of immune bodies in suprarenalectomized rats than in normal rats. There may, however, be no actual loss of production of immune bodies, but a diminished release of these antibodies into the blood stream. The injection of large quantities of fluid containing isotonic solutions of sodium salts restores the water balance in the body to normal by promoting diuresis and supplying fluid in a form that can be retained in the tissues. The antibody-forming mechanism is thus restored to normal. The rôle of the suprarenal gland in the formation of antibodies appears to be intimately connected with the maintenance of water balance. This observation is of importance in the interpretation of certain phenomena in acute infections. It is a matter of empiricism that forcing fluids is beneficial in the treatment of severe infections and of extensive burns of the skin. It is known that in burns and in many acute infections the suprarenal glands are severely injured. The injury may result in a disturbance of the water balance of the tissues and of the antibody-forming capacity of the body. This disturbance may be corrected to some extent by the parenteral and oral administration of large quantities of physiologic solution of sodium chloride.

It may be concluded that suprarenalectomy is followed by a disturbance in the antibody-forming mechanism of the tissues. The suprarenal gland plays a rôle in the water metabolism of the tissues. Restoration of the water exchange to a normal level is sufficient to restore the antibody-forming capacity to normal. The rôle of the suprarenal cortex in the formation of antibodies is therefore an indirect one, dependent on the influence of the cortex on the water balance in the tissues.

II. RELATION OF THE SUPRARENAL GLANDS TO ANAPHYLAXIS

Képinow [26] found that the removal of one suprarenal gland and of the greater part of the other makes guinea-pigs more susceptible to anaphylactic shock, especially to active anaphylaxis.

25. Baumann, E. J., and Kurland, Sarah: J. Biol. Chem. **71**:281, 1927.

26. Képinow, L.: Compt. rend. Soc. de biol. **87**:327, 1922.

Ten unilaterally suprarenalectomized guinea-pigs and seven normal controls were sensitized with horse serum, and from sixteen to eighteen days later the other suprarenal gland of the animals operated on previously was partially removed. Six days after the second operation, varying amounts of horse serum were injected intra-arterially both into the suprarenalectomized animals and into the controls. The normal animals presented the symptoms characteristic of anaphylactic shock and died following the injection of 0.1 cc. of horse serum. The animals that had been operated on were killed by 0.025 cc. of horse serum. In another series of guinea-pigs, the removal of one gland and part of the other was done at the same time; the animals were sensitized with an injection of serum fifteen days later, and subsequently tested as in the first series. The controls were killed by a second injection of 0.2 cc. of horse serum, and the animals that were operated on succumbed after an injection of 0.025 cc., one eighth the amount necessary to kill a normal guinea-pig. In guinea-pigs passively sensitized by the injection of serum of rabbits actively sensitized to horse serum, the amount of serum necessary to produce shock was the same in the controls as in the animals with suprarenal insufficiency.

Bilaterally suprarenalectomized rats show markedly increased susceptibility to anaphylactic shock produced by intraperitoneal injections of horse serum (Flashman,[27] Wyman [28]). This effect is obtained whether the animals are sensitized before or after suprarenalectomy.

The normal albino rat is very resistant to anaphylaxis. This reflects in part the high degree of natural resistance to all toxins and poisons, but the rat is known to form precipitins poorly (Longcope). Parker and Parker, however, in 1924, showed that anaphylactic shock can be produced in the white rat after both active and passive sensitization.

In studying the relation of suprarenal insufficiency to anaphylaxis, Wyman [28] used adult rats, from 5 to 12 months old. The rats were sensitized by giving three intraperitoneal injections of 1 cc. of horse serum at two day intervals. The test dose of 1 cc. of horse serum was given on the tenth, eleventh or twelfth day after the last sensitizing dose. Of 25 doubly suprarenalectomized rats sensitized with horse serum, 36 per cent died of anaphylactic shock following the test dose, 20 per cent had severe symptoms, and 32 per cent had slight symptoms. In 12 of the cases, the first sensitizing dose was given from twelve to sixteen days after suprarenalectomy. The test dose was given from twenty-three to twenty-seven days after operation. Following the test dose, 5 of the 12 animals had slight symptoms, 2 had moderate symptoms, 3 had severe symptoms (2 of these died in twelve hours), and 2 died sixty and one hundred and forty-seven minutes after the injection.

In the 13 other cases the first sensitizing dose was given from eighty-five to one hundred and sixty-eight days after suprarenalectomy and the test dose was given ten or eleven days later. Three animals had slight symptoms, 1 had moderate symptoms, 2 had severe symptoms, and 7 died from thirty to one hundred and forty-three minutes after the injection.

A group of 29 normal rats were sensitized by injections of horse serum and tested twelve days later. There were slight or no symptoms, and none of the

27. Flashman, D. H.: J. Infect. Dis. **38**:461, 1926.
28. Wyman, L. C.: Am. J. Physiol. **89**:356, 1929.

animals died. Of 15 of these rats which were suprarenalectomized after the test injection, 12 died of anaphylactic shock following the injection of a second test dose from seven to ten days after the operation. It is interesting that no correlation was found between the presence or absence of gross accessory cortical tissue or the time of survival after operation and the susceptibility to anaphylactic shock.

Of 15 suprarenalectomized rats having autoplastic cortical transplants and in some cases gross accessory cortical tissue as well, 40 per cent died of anaphylactic shock following sensitization and the injection of a test dose of horse serum. From these experiments, Wyman concluded that the increased susceptibility to anaphylactic shock must be due to medullary insufficiency. An attempt to reduce the susceptibility of suprarenalectomized rats to anaphylactic shock by means of repeated injections of epinephrine chloride solution gave evidence of little or no protection.

The work of Wyman conclusively demonstrates the increased susceptibility of suprarenalectomized rats to anaphylaxis. The evidence does not prove that the medullary deficiency is responsible, though it may play a rôle.

The failure of cortical rests or transplants to protect does not exclude the fact that the normal cortex may be essentially responsible for the high degree of resistance of the rat to anaphylaxis. Though cortical rests in suprarenalectomized animals may function sufficiently to prolong life, they do not appreciably raise the resistance of these animals to severe intoxication. We have found this to be true in histamine poisoning. Nevertheless the administration of cortical hormone raises the resistance of suprarenalectomized rats to the level of normal rats.

III. RELATION OF THE SUPRARENAL GLANDS TO NATURAL AND ACQUIRED RESISTANCE

Though the increased susceptibility of suprarenalectomized animals to toxins and poisons was suggested in fragmentary, poorly controlled work by French investigators,[29] Lewis[30] first demonstrated, in 1921 and 1923, the marked sensitivity of suprarenalectomized rats to intoxication with cobra venom, curare, veratrine, papaverine, codeine, morphine, digitoxin, epinephrine and diphtheria toxin. There was no depression in the resistance of suprarenalectomized animals to picrotoxin and strychnine. He observed that the resistance is lowered soon after suprarenalectomy and gradually diminishes until it disappears. The resistance of suprarenalectomized rats to morphine is four hundred

29. Abelous, J. E.: Compt. rend. Soc. de biol. **47**:458, 1895. Boinet, E.: ibid. **48**:364, 1896. Langlois and Charrin: ibid. **48**:708, 1896. Oppenheim, M. R.: ibid. **53**:314 and 316, 1901.

30. (*a*) Lewis, J. T.: Rev. Asoc. méd. argent. **35**:529, 1921; (*b*) Am. J. Physiol. **64**:506, 1923.

times lower than that of normal rats. The problem was extensively studied in Marine's laboratory for many years. Scott [31] confirmed the susceptibility of suprarenalectomized rats to morphine. Belding and Wyman [32] extended the observations to diphtheria toxin and noted that rats without suprarenal glands were twice as susceptible as normal rats. Marked depression in resistance to typhoid vaccine was noted by Jaffe and Marine,[19] and Jaffe [33] demonstrated a definite protective action afforded by autoplastic transplants of cortical suprarenal tissue prior to suprarenalectomy. Further studies were made with cystine, glutathione and cyanides by Voegtlin, Johnson and Dyer,[34] and these confirmed the early work on the significance of the suprarenal cortex in resistance.

An effort to standardize a test for suprarenal insufficiency in the rat was made by Marmorston-Gottesman and Gottesman.[35] Of all the drugs thus far used in testing the resistance of suprarenalectomized rats, histamine was found to be most satisfactory. It is readily obtainable and comparatively stable and produces characteristic symptoms. The minimum lethal dose for a given strain of rats can be established within narrow limits, and the difference between the minimum lethal dose for normal and for suprarenalectomized rats is comparatively great (1:10). Banting and Gairns [36] found that suprarenalectomized dogs are about thirty times more susceptible to histamine than are normal dogs.

Marmorston-Gottesman and Gottesman [35] demonstrated the presence of a latent period after suprarenalectomy during which time resistance is still relatively high. The marked drop in resistance does not occur until about the fifth day after the operation. The height of susceptibility is reached between the fifth and eighth day.

Of 18 suprarenalectomized rats into which 100 mg. of histamine acid phosphate per kilogram was injected between the first and the fourth day after removal of both glands, only 5 were killed, whereas of 31 suprarenalectomized rats inoculated five, six, seven and eight days after operation, 24 were killed.

The resistance of suprarenalectomized rats is strikingly lowered during all periods after the operation, but the depression is greatest at the end of the first week. The drop in resistance occurs in all rats regardless of the presence of accessory cortical tissue. Such severe procedures as bilateral nephrectomy, however, fail to affect the resistance

31. Scott, W. J. M.: J. Exper. Med. **38**:543, 1923.
32. Belding, D. L., and Wyman, L. C.: Am. J. Physiol. **78**:50, 1926.
33. Jaffe, H. L.: Am. J. Path. **2**:421, 1926.
34. Voegtlin, Carl; Johnson, J. M., and Dyer, H. A.: J. Pharmacol. & Exper. Therap. **27**:467, 1926.
35. Marmorston-Gottesman, J., and Gottesman, J.: J. Exper. Med. **47**:503, 1928.
36. Banting, F. G., and Gairns, S.: Am. J. Physiol. **77**:100, 1926.

of the rat, though death supervenes in seven or eight days (Marmorston-Gottesman and Gottesman [37]).

The use of the rat in studying problems of resistance following suprarenalectomy has many advantages. In our experience with rats from original Wistar Institute stock maintained in this laboratory for about ten years, under standard dietetic and environmental conditions the percentage of animals surviving bilateral suprarenalectomy for two weeks or longer was about 90. These observations are based on an experience with over 1,000 rats.

There are conflicting reports in the literature on the survival capacity of rats following suprarenalectomy. Most authors agree that a very large percentage of rats survive the removal of the suprarenals for a considerably longer period than other mammals (Lewis,[30b] Scott,[31] Jaffe and Marine,[19] Jaffe,[33] Wyman,[28] Perla and Marmorston and others). Jaffe observed that in a series of 90 suprarenalectomized rats, 35 per cent died within thirty days, most of them before the thirteenth day; 46 per cent died in seven months, and 19 per cent remained unaffected and presented a large amount of accessory cortical tissue when killed.

Pencharz, Olmsted and Giragossintz,[38] on the other hand, observed that all of a series of 62 suprarenalectomized rats died in from two to eighteen days with no survivals beyond this period. Rats from 3 to 4 weeks of age were utilized by Kutz [39] for the determination of the potency of cortical extracts.[4] He observed that 56 of 57 suprarenalectomized rats died by the tenth day. Freed, Brownfield and Evans [40] reported that suprarenalectomy in rats is fatal in all instances. Firor and Grollman,[41] in a recently published article, concluded that the rat presents no exception to the fact that suprarenalectomy in mammals is fatal.

The survival capacity of rats following suprarenalectomy is dependent on the varying amounts of microscopic rests of cortical cells in the retroperitoneal space from the region of the suprarenal gland to the bifurcation of the aorta. Gross accessory tissue is not frequently observed, although serial sections of the retroperitoneal tissue show accessory cortical tissue in a very high percentage of rats. It is impossible to remove all the accessory cortical tissue, and one must, therefore, limit oneself to removal of the suprarenal glands if one is to observe

37. Marmorston-Gottesman, J., and Gottesman, J.: Proc. Soc. Exper. Biol. & Med. **24**:45, 1926.

38. Pencharz, R.; Olmsted, J. M. D., and Giragossintz, G.: Physiol. Zoöl. **4**:501, 1931.

39. Kutz, R. L.: Proc. Soc. Exper. Biol. & Med. **29**:91, 1931.

40. Freed, S. C.; Brownfield, B., and Evans, H. M.: Proc. Soc. Exper. Biol. & Med. **29**:1, 1931.

41. Firor, W., and Grollman, A.: Am. J. Physiol. **103**:686, 1933.

the effects of this operation in the rat. The conflicting reports on the survival capacity of rats may be due in part to faulty technic in the operation. (Suprarenalectomy is extremely likely to produce shock and must be done skilfully with a minimum amount of trauma and tugging at the tissues.) The poor survival capacity may be due to careless after-care, as suprarenalectomized rats are extremely susceptible to the effects of cold. In extremely young rats (under the age of 4 weeks) a much higher mortality occurs than in older animals. At from 7 to 8 weeks of age rats show an excellent capacity for surviving the operation, in our experience, and the resistance may be somewhat higher than that of adult rats one week after operation. Undoubtedly, different strains of rats possess varying amounts of cortical tissue. It is possible that some strains possess no such accessory cortical tissue and do not survive suprarenalectomy any better than the larger mammals. There are other factors which may influence the period of survival of suprarenalectomized rats. We have observed that the use of an artificial diet adequate in all respects, according to present knowledge, seems to lower the capacity for survival of rats following the removal of the suprarenals. Of a series of 20 suprarenalectomized rats from 2 to 3 months old fed on our usual mixed diet of scraps of meat, hominy, rolled oats, milk, bread, salt and greens, 17 survived for a month, at which time they were killed. Of a group of 15 rats fed on a completely adequate artificial diet, composed of casein, cornstarch, yeast and MacCallum's salt mixture, butter fat, viosterol and orange juice, only 1 survived for three weeks, and of the remaining 14, 10 died from the seventh to the ninth day and 3 from the seventh to the twentieth day. Although artificial diets such as these may be adequate when gaged by curves of growth and by the reproductive capacity of the animals, under conditions of marked physiologic strain they may prove to be inadequate in some still unknown respect. The importance, therefore, of maintaining a uniform strain of rats bred in the laboratory and kept under identical environmental and dietetic conditions cannot be overemphasized.

It has been our experience from a large series of observations that in spite of the presence of microscopic cortical tissue in the rat, all rats of our stock one week after operation show a profound drop in the natural resistance to poisons and infections. Although the small amount of accessory tissue may be sufficient to maintain life for a comparatively long period, it is insufficient to maintain the normal natural resistance of the animal.

The decrease in the resistance of suprarenalectomized rats to poisons such as cyanide, nicotine, acetylcholine, histamine, curare, morphine, snake venom, diphtheria toxin, chloral hydrate and typhoid vaccine has been demonstrated by numerous investigators. The development of a test of the degree of suprarenal insufficiency in the rat, a mammal that

lends itself to laboratory standardization, was of considerable importance in later work in this field.

The study of the problem was broadened and extended into the field of infections by the work of Perla and Marmorston-Gottesman [42] who studied the effects of suprarenalectomy on the resistance of the rat to a protozoan infection caused by Trypanosoma lewisi and to Bartonella muris anemia, two diseases native to the rat.

In the experiments with T. lewisi,[42a] 18 adult rats were suprarenalectomized, and in 5 the suprarenal areas were traumatized. Six days after the operation each rat was given intraperitoneally 1 cc. of a 10 per cent dilution of whole blood drawn from a rat infected with T. lewisi. Counts of the trypanosomes in the peripheral blood were made at frequent intervals.

Sixty-seven per cent of the rats died from two to nineteen days after the injection. The average duration of life of the rats in which the infection proved fatal was five and eight-tenths days. Though the disease is fatal in about 70 per cent of suprarenalectomized rats, it is not fatal in normal rats. Despite this high mortality, the infection, as characterized by the rate of growth of the trypanosomes, does not differ essentially from the infection in normal rats. Neither the reproduction-inhibiting antibody (Taliaferro [43]) nor the trypanolytic factor is diminished by suprarenalectomy. Apparently the *toxic* effect of the infection is lethal in these animals. Suprarenalectomy, further, diminishes the degree of splenic response as estimated by the size of the spleen but does not alter the reaction of the reticular and endothelial elements of the spleen or of the lymphoid tissue to infection with T. lewisi.

One infection with T. lewisi confers a permanent immunity on normal rats. It is of significance that suprarenalectomy does not break down the permanent immunity acquired as a result of a first infection. The natural susceptibility of the rat to various toxins, poisons and infections is markedly increased by suprarenalectomy. But the acquired immunity established as a result of a first infection is uninfluenced.

In subsequent communications further data were presented on the effect of bilateral suprarenalectomy in the rat on natural and acquired resistance to B. muris anemia.[42b]

The rat is spontaneously infected with B. muris between the fourth and fifth weeks of life. It becomes a carrier and acquires immunity. The spontaneous recurrence of infection following splenectomy with the development of anemia

42. (*a*) Marmorston-Gottesman, J.; Perla, David, and Vorzimer, Jefferson: J. Exper. Med. **52**:587, 1930. (*b*) Marmorston-Gottesman, J., and Perla, David: ibid. **55**:109, 1932.

43. Taliaferro, W. H.: The Immunity of Parasitic Infections, New York, Century Company, 1929.

in the adult rat of carrier stock is indicative of a depression in the acquired resistance to B. muris. (For a review of this subject, see papers by Perla and Marmorston-Gottesman,[42b] Lauda [44] and Reitano [45]).

Ten rats, 3 months of age, were suprarenalectomized. On the sixth day after suprarenalectomy, each was given intraperitoneally 2 cc. of whole blood of anemic adult splenectomized rats. No anemia developed in any of the rats. Ford and Eliot [46] showed that 0.0001 cc. of blood of an anemic rat is sufficient to transmit the anemia to splenectomized rats of noncarrier stock. The suprarenalectomized rats of carrier stock, therefore, withstand a quantity of infecting material twenty thousand times as great as is sufficient to produce anemia in the splenectomized rat of noncarrier stock. The acquired resistance to B. muris conferred on rats of carrier stock by a first infection in early life, though strikingly depressed by splenectomy, is uninfluenced by suprarenalectomy.

The effect of suprarenalectomy on the natural resistance to B. muris was studied in rats of Wistar Institute stock, noncarriers of B. muris. In these rats splenectomy is not followed by B. muris anemia, but anemia will develop if they are subsequently exposed to rats of carrier stock for a few days. Of 10 suprarenalectomized rats of Wistar Institute stock, 8 died within three days following the injection of infective material and 2 on the fifth and sixth days. In most instances the rats died before sufficient time had elapsed for the development of severe anemia. Death was apparently caused by toxemia. In rats surviving longer than two days anemia developed. Though severe anemia developed after the injection of the same amount of infecting material into the control rats of Wistar stock that had not been operated on, all of these recovered. It is apparent that the natural resistance to infection with B. muris is lowered by suprarenalectomy. Although the rapidity with which the anemia developed was no greater nor was the disease more severe in the suprarenalectomized than in the normal rats, all the suprarenalectomized rats died of toxemia. (The mortality from B. muris anemia in splenectomized rats of carrier stock is about 30 per cent.) The nature of the rôle of the suprarenal glands in natural resistance to this infection is of a general character. There is no change in the type of reaction in the tissues following infection in suprarenalectomized rats, but there is an increased susceptibility to toxic substances produced in the course of a first infection. However, the *acquired* resistance to B. muris conferred by a first infection is not broken down

44. Lauda, E.: Bartonella, in Kolle, Kraus and Uhlenhuth: Handbuch der pathogenen Mikroorganismen, ed. 3, Jena, Gustav Fischer, 1930, vol. 8, no. 44, p. 1073.

45. Reitano, U.: Boll. Ist. sieroterap. milanese **9**:325, 1930.

46. Ford, W. W., and Eliot, C. P.: Am. J. Hyg. **12**:669, 1930.

by subsequent suprarenalectomy, though the *natural* resistance is markedly depressed.

In an effort to determine further the relation of the suprarenal gland to *acquired resistance,* the effect of suprarenalectomy in rats on the acquired immunity to typhoid vaccine, established by previous repeated injections of vaccine, was determined (Marmorston-Gottesman and Perla [47]).

In a preliminary experiment the minimum lethal dose of a batch of typhoid vaccine for suprarenalectomized rats was determined. This was found to be 0.5 cc. Fourteen rats received three intraperitoneal injections of typhoid vaccine at weekly intervals (0.5 cc. and 1 cc.). Five days after the last injection these 14 rats, together with 10 normal rats, were suprarenalectomized. On the sixth day following the operation, 8 immunized suprarenalectomized rats were given intraperitoneally 5 cc. of typhoid vaccine, and 6, 1 cc. All the unimmunized rats were given twice the minimum lethal dose (1 cc.). Within twelve hours all the unimmunized rats died. Those rats that had been immunized and subsequently suprarenalectomized survived the injection of a quantity ten times the minimum lethal dose for suprarenalectomized rats.

Suprarenalectomy does not apparently diminish the acquired resistance to typhoid vaccine.

The striking difference in the effect of suprarenalectomy on acquired and natural resistance was demonstrated in infection with B. muris, with T. lewisi and with typhoid vaccine. Though suprarenalectomy markedly depressed the natural resistance of the rat to infection with B. muris, with T. lewisi and with typhoid vaccine, it did not influence the acquired resistance to these antigenic substances established by previous spontaneous or induced infection or by previous injection of the antigen. These observations indicate that once a cellular or a humoral immunity to an infection or an antigenic substance is established, this acquired resistance cannot be broken down by subsequent suprarenalectomy.

The depression in *natural resistance* that follows bilateral suprarenalectomy is a general phenomenon as is shown by the increased susceptibility to toxins and poisons and to bacterial and protozoan infections. It is probably a manifestation of a profound disturbance in cellular metabolism.

These studies strongly suggest that acquired resistance and natural resistance are dependent on different physiologic processes and are not merely quantitative variations of the same process as is generally assumed.

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47. Marmorston-Gottesman, J., and Perla, David: Proc. Soc. Exper. Biol. & Med. **28**:648, 1931.

Recently Steinbach studied the effect of suprarenalectomy on tuberculous infection in immature albino rats.[48] It is well known that the albino rat is highly resistant to the human and the bovine tubercle bacillus though it is readily infected with the avian strain.

Of 19 immature suprarenalectomized rats into which was injected 1 mg. of bovine tubercle bacillus B, 79 per cent showed definite evidences of tuberculosis in the abdominal organs but none in the lungs. No evidence of tuberculosis had been observed in 34 normal rats similarly inoculated, with a single exception. Of 18 suprarenalectomized rats inoculated with human tubercle bacilli on the fifth day after operation and killed after from four to sixty-five days, none showed evidence of tuberculosis, although acid-fast organisms could be demonstrated in all the tissues examined. Of 18 controls inoculated with 1 mg. of human tubercle bacilli (H 37), none showed evidences of tuberculosis. A small series of rats (4) received intraperitoneal injections of enormous doses of human tubercle bacilli (25, 50, 75 and 100 mg.). All 4 animals were killed in ninety days. The organs contained numerous bacilli, but no lesions were observed.

With a virulent avian strain, Steinbach observed that tuberculous lesions develop in 100 per cent of suprarenalectomized rats, but in only 50 per cent of normal controls.

From his studies, Steinbach concluded that bilateral suprarenalectomy lowers the natural resistance of albino rats to avian and bovine tuberculosis. The rat is normally highly refractory to infection with human and with bovine tubercle bacilli. Suprarenalectomy apparently does not affect the high natural resistance of the rat to human tubercle bacilli.

Perla and Marmorston, in an independent study (unpublished work) on the effect of suprarenalectomy on tuberculous infection in albino rats essentially confirmed these observations. However, they observed infections in suprarenalectomized rats with human tubercle bacilli as well.

Normal adult rats showed microscopic evidences of tuberculosis when given 1 mg. of bovine tubercle bacilli intraperitoneally within one month. Of 5 rats inoculated with 1 mg. of bovine tubercle bacilli C, a virulent strain, seven days after suprarenalectomy and killed thirty-one days later, 3 showed evidence of tuberculosis. Of 5 controls, only 1 showed evidence of tuberculosis in this interval. Of 5 suprarenalectomized rats inoculated with 1 mg. of human (P 15 B) tubercle bacilli B, seven days after operation and killed thirty-one days later, two showed evidence of tuberculosis in the abdominal organs and mediastinal nodes. In 3 controls tuberculosis did not develop. Of 4 suprarenalectomized adult rats into which was injected 1 mg. of avian tubercle bacilli (no. 112) all presented evidence of tuberculosis within one month. Of 4 controls, tuberculosis developed in 2 in the same period.

In adult rats suprarenalectomy increased the susceptibility to all three types of tubercle bacilli, avian, human and bovine.

48. Steinbach, M. M.: Proc. Soc. Exper. Biol. & Med. **27**:142, 1929.

Of interest is a second group of experiments in which the inoculated animals were killed after six months' observation. Thirteen rats were suprarenalectomized. Seven days later, 1 mg. of bovine tubercle bacilli C was injected into 8 of these and 5 mg. into the others. Five controls received 5 mg. of the same strain, and 8 controls, 10 mg. Six months later all were killed. Of the 5 controls that received 5 mg., 1 showed evidence of tuberculosis. Of the 8 controls that received 10 mg., 5 showed evidence of tuberculosis. Of the 8 suprarenalectomized rats into which 1 mg. was injected, none showed evidence of tuberculosis. Of the 5 suprarenalectomized rats given 5 mg., one showed evidence of tuberculosis. This experiment suggests that the tuberculosis which readily develops in suprarenalectomized rats one month following the injection of 1 mg. of bovine strain C apparently may heal without scarring and after six months no trace may be observed. The tuberculous lesions in the rat consist of groups of mononuclear phagocytes with little or no lymphocytic reaction. Some of these cells are fused to form giant cells with nuclei uniformily scattered, and they contain acid-fast organisms. Caseation and necrosis were observed only in tuberculosis produced by the avian strain.

IV. THE CORTICAL HORMONE AND NATURAL RESISTANCE

The mass of experimental evidence definitely establishes the significance of the suprarenal gland in the mechanism of *natural* resistance. It is important to determine whether the depression in resistance is associated with removal of the cortex or the medulla. It has been repeatedly shown that accessory chromaffin tissue exists in the body and that removal of the suprarenals does not destroy all this tissue.

Is the increased susceptibility of suprarenalectomized rats to toxins and infections, then, to be considered a manifestation of medullary or of cortical insufficiency, or of both? Three methods of approach have been used in an attempt to answer this question.

1. The effect of injections of the medullary secretion, epinephrine, on the resistance of suprarenalectomized rats to such poisons as histamine was studied by Wyman [49] and independently by Perla and Marmorston-Gottesman.[50] Wyman reported that he was able to protect suprarenalectomized rats against histamine poisoning by intraperitoneal injections of epinephrine.

As indicated in his data, 34 rats were treated with epinephrine. One group of 12 rats received three intraperitoneal injections of epinephrine prior to the injection of histamine. Of this group, 9 rats, or 75 per cent, survived. However, of 22 rats in a second group receiving a single intraperitoneal injection of epinephrine ten minutes prior to the injection of histamine, 3, or 13 per cent, survived. This is approximately the percentage of survival of untreated suprarenalectomized rats that received the same quantity of histamine. Wyman expressed the belief that the small amount of epinephrine present in the blood stream following its injection intraperitoneally is responsible for its protective action against the histamine

49. Wyman, L. C.: Am. J. Physiol. **87**:29, 1928.

50. Perla, David, and Marmorston-Gottesman, J.: Am. J. Physiol. **89**:152, 1929.

and is dependent on the immediate antagonistic effect of these two drugs. He maintains that the susceptibility to histamine poisoning of suprarenalectomized rats is due to insufficiency of the medulla and not of the cortex.

Perla and Marmorston-Gottesman [50] found that subcutaneous injections of epinephrine administered twice daily during seven days following suprarenalectomy afford protection to rats against a lethal dose of histamine in 50 per cent of cases. The last injection of epinephrine is administered two hours prior to the injections of histamine.

If the epinephrine is discontinued twenty-four hours before the injection of histamine its protective effect is markedly decreased. A single injection of epinephrine given two hours prior to the injection of histamine affords no protection to suprarenalectomized rats. The protective action of repeated subcutaneous injections of epinephrine against histamine poisoning in suprarenalectomized rats is in part due to a true hormonal effect and is not entirely dependent on the pharmacologic antagonistic action of epinephrine to histamine. It is probable that the medulla plays some part, if only a slight one, in the depressed resistance following suprarenalectomy.

2. Studies have been made on the effect of the presence of cortical rests, of removal of the cortex alone and of autoplastic cortical transplants on the resistance of suprarenalectomized rats. It has been our experience that even a small fragment of cortical tissue left in situ is sufficient to protect suprarenalectomized rats against injections of lethal doses of histamine. Kellaway and Cowell [51] showed that if the cortex of both suprarenal glands of cats is destroyed but the medulla of one gland is left intact the animals show marked hypersensitivity to small doses of histamine. They maintained that deficiency of the cortex plays an important part in the susceptibility of suprarenalectomized animals to histamine. Wyman [49] was unable to observe protection against histamine in suprarenalectomized rats by autoplastic transplants of small fragments of cortical tissue. Jaffe and Plavska,[52] continuing earlier observations on the susceptibility of suprarenalectomized rats to typhoid vaccine (Marine and Jaffe),[19] noted that in the absence of accessory cortical tissue the sensitivity of rats to typhoid continued for as long as five months after operation. Suprarenalectomized rats that have a relatively high degree of resistance invariably possess gross cortical accessory tissue. In the absence of gross accessory tissue, autoplastic cortical transplants will protect suprarenalectomized rats against typhoid

51. Kellaway, C. H., and Cowell, S. J.: J. Physiol. **57**:82, 1922.

52. Jaffe, H. L., and Plavska, Alexandra: Proc. Soc. Exper. Biol. & Med. **23**:528, 1926.

vaccine in amounts otherwise lethal for suprarenalectomized rats. The evidence strongly suggests the greater significance of the cortex in the mechanism of resistance.

3. The discovery of the suprarenal cortical hormone by Hartman [53] and by Swingle and Pfiffner [54] afforded an opportunity to determine the effect of cortical hormone on the depressed resistance to toxins and infections in suprarenalectomized animals. These studies were made by Perla and Marmorston-Gottesman [55] and independently by Hartman and Scott.[56]

The protective effect of an extract of the cortex of the suprarenal gland prepared by us according to the method of F. A. Hartman was determined with typhoid vaccine.[55a] The cortical extract was administered intraperitoneally twice daily from the day of operation for a period of six days; the typhoid vaccine was then injected (1 cc. of extract was equivalent to 40 Gm. of cortex).

The minimum lethal dose of a batch of typhoid vaccine for suprarenalectomized rats was determined. The experimental animals were divided into four groups. One group of 17 rats received cortical extract twice daily from the day of operation to the end of the experiment. Of these, 4 rats on the sixth day were given 1 minimum lethal dose, 5, 2 minimum lethal doses, 4, 4 minimum lethal doses and 4, 6 minimum lethal doses of typhoid vaccine. A second group of 10 rats received equivalent amounts of salt solution. On the sixth day these were given 1 minimum lethal dose of typhoid vaccine. A third group of rats were untreated, and on the sixth day after operation these animals were given 1 minimum lethal dose of typhoid vaccine. A fourth group of 4 rats received cortical extract during only the twenty-four hour period before and after the injection of 1 minimum lethal dose of typhoid vaccine on the sixth day.

The rats that had been repeatedly inoculated with cortical extract survived as much as 4 minimum lethal doses of typhoid vaccine. The rats of the fourth group, which had received cortical extract only during the last twenty-four hour period, survived 1 minimum lethal dose of typhoid vaccine. The controls were killed by 1 minimum lethal dose of vaccine.

Independently Hartman and Scott [56] likewise observed the effect of cortical injections in raising the resistance of suprarenalectomized rats to typhoid vaccine. These experiments indicate that the cortical extract of Hartman raises the resistance of suprarenalectomized rats. It was suggested that a cortical extract may be biologically assayed by

53. Hartman, F. A.: Endocrinology **14**:229, 1930.

54. Swingle, W. W., and Pfiffner, J. J.: Science **71**:321, 1930.

55. (*a*) Perla, David, and Marmorston-Gottesman, J.: Proc. Soc. Exper. Biol. & Med. **28**:475, 1931; (*b*) **28**:650, 1931; (*c*) **28**:1022, 1931.

56. Hartman, F. A., and Scott, W. J. M.: Proc. Soc. Exper. Biol. & Med. **28**:478, 1931.

determining the minimal protecting amount to be administered within twenty-four hours before and after the injection of the minimal lethal dose of typhoid vaccine for suprarenalectomized adult rats on the sixth day after suprarenalectomy.

In subsequent experiments the effect of injections of cortin on the resistance of suprarenalectomized rats to histamine was studied.[57]

Adult suprarenalectomized rats are killed by from 100 to 120 mg. of histamine per kilogram of body weight administered on the sixth day after operation. Normal rats survive from 700 to 900 mg. per kilogram. For 6 week old suprarenalectomized rats the minimum lethal dose of histamine is from 150 to 200 mg. per kilogram. Fourteen suprarenalectomized rats received injections of 0.5 cc. of cortin twice daily (1 cc. = 40 Gm. of cortex). On the sixth day, 6 rats received 150 mg. of histamine per kilogram, 3, 200 mg.; 3, 300 mg., and 2, 500 mg. All survived.

The daily injections of cortin raised the resistance to at least 3 minimum lethal doses of histamine. The maximal amount of histamine that suprarenalectomized rats treated with cortin will survive was later determined and it was observed that the resistance of suprarenalectomized rats could be raised almost to the normal level [55c] when 2 cc. of cortin (equivalent to 80 Gm. of cortex) was administered daily during the first two weeks following operation.

Five rats thus treated were given 600 mg. of histamine per kilogram on the sixth day. All survived. Three were given 700 mg. of histamine per kilogram, and of these, 2 survived. Of 8 given 800 mg. per kilogram, 3 survived. Of 3 controls given 900 mg. per kilogram, 2 survived, and of 3 controls given 950 mg. per kilogram, 1 survived.

From these results it is apparent that it is possible in many instances to raise the resistance of suprarenalectomized rats almost to the level of the resistance of normal rats by repeated injections of large amounts of cortin. The effect of the cortical hormone is specific. Previous work had shown that large amounts of saline solution have no demonstrable effect on the resistance of suprarenalectomized rats. Repeated injections of epinephrine have only a slight effect.

An extract of the spleen made in the exact manner as the cortical extract failed to produce any increase in the resistance of suprarenalectomized rats. The anterior pituitary hormone of Doisy (theelin) did not raise the resistance of suprarenalectomized rats. With the male sex hormone (Funk and Harrow) negative results were obtained.

We believe, therefore, that the action of cortin on the resistance of suprarenalectomized rats to histamine and other toxins and poisons is

57. Perla and Marmorston-Gottesman (footnote 55 *b* and *c*).

a measure of the specific activity of the life-prolonging hormone of the suprarenal cortex.[58]

It is evident that the marked susceptibility of suprarenalectomized rats to histamine poisoning is not due to insufficiency of epinephrine, or is so only in part, as maintained by Wyman, but is primarily the result of cortical insufficiency.

The decrease in natural resistance that follows suprarenalectomy in animals is due primarily to *cortical insufficiency,* and repeated injections of the cortical hormone increase the resistance of the suprarenalectomized animal.

The discovery of a cortical hormone and the demonstration that it raises the resistance of rats with suprarenal insufficiency suggest further research in the therapeutic use of cortical extracts in the treatment of human infectious disease. In many infectious diseases and in severe burns and intoxications the cortex is markedly injured. It is probable that injections of the cortical hormone may prove of great value in such conditions. Few studies of this nature have been made. Whitehead and Smith [59] used injections of cortical extract (Swingle and Pfiffner [54]) in the treatment of patients with severe infections with somewhat encouraging results.

Five patients were treated. In the first patient, who was suffering from typhoid fever, 2 cc. of the extract (equivalent to 100 Gm. of cortex) was given on the eleventh day. The temperature became normal on the second day and remained so during the next fourteen days. The second patient, with undulant fever of six weeks' duration, was given several injections, and the temperature returned to normal within two days. The third patient, who had postoperative erysipelas, was unsuccessfully treated. He died after temporary improvement. The fourth patient, who had lymphangitis of the hand with resultant sepsis, was cured after one injection of 2 cc. of cortical hormone. In the fifth patient, a virulent ethmoid sinus infection cleared after several injections of extract. This patient remained under observation for one month.

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58. It was suggested that the protective action of cortical extracts against histamine poisoning in suprarenalectomized rats provides a better means of biologically assaying the potency of such extracts than does typhoid vaccine, which was previously suggested. Histamine is a standard chemical that varies little in toxicity. The amount of cortical extract (injected intraperitoneally into suprarenalectomized albino rats on the fifth and sixth days after operation) necessary to protect these rats against 200 mg. of histamine per kilogram of body weight may be considered as a standard unit. DeMeio and Lewis (Compt. rend. Soc. de biol. **111**:822, 1932) confirmed these observations on the effect of cortical extracts on the resistance of suprarenalectomized rats to poisons. Repeated injections of the cortical extract of Swingle and Pfiffner [54] increased the resistance of suprarenalectomized rats to morphine hydrochloride. These authors suggested assaying cortical extracts by this method.

59. Whitehead, R. W., and Smith, C.: Proc. Soc. Exper. Biol. & Med. **29**: 672, 1932.

These instances are too few to be of value in determining the use of cortin in infections, but were reported only as the results of a preliminary investigation. A wide trial of cortin therapeutically is imperative, but at present the cost of extraction is prohibitive. A method of obtaining larger yields more simply must be discovered before this important hormone may be available for general use.

V. SIGNIFICANCE OF THE DEPRESSION IN NATURAL RESISTANCE FOLLOWING SUPRARENALECTOMY

The depression in natural resistance following suprarenalectomy in animals is a general phenomenon, not specific for any one type of intoxication. It was believed previously that the suprarenals possess the capacity for direct detoxification of poisons somewhat as the liver does. The evidence for this hypothesis was gathered from the pathologic changes which usually occur in the cortex of the suprarenals in acute and chronic infections, in acute intoxications and in severe burns. It was, further, well established that suprarenalectomized cats, dogs and rats are extremely susceptible to spontaneous infections of the respiratory tract. The detoxification theory, however, has been discarded, since it was found contrary to the observations of many investigators. Marine [3] and others found no diminution in the toxicity of diphtheria toxin when it was mixed in vitro with emulsions of suprarenal cortex

The general character of the diminution in resistance that follows suprarenalectomy in animals suggests that it may be a manifestation of an interference with the normal cellular metabolism which occurs with suprarenal cortical insufficiency. When this disturbance is relieved by the administration of the life-prolonging hormone of the cortex the natural resistance of the animal may be raised.

A brief consideration of certain phases of the physiology of the suprarenal cortex, while not directly pertinent to this review, may aid in understanding the relation of the mechanism of resistance to cortical function.[60] The studies of the past decade on the physiology of the suprarenal cortex have revealed its fundamental importance in the maintenance of life.

Repeated injections of the cortical hormone, isolated independently by Hartman [53] and by Swingle and Pfiffner,[54] prolong the lives of suprarenalectomized cats and dogs and of patients suffering with Addison's disease.[61] The nature of this controlling mechanism is still obscure.

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60. For a review of the literature on the physiology and pathology of the suprarenal glands, the reader is referred to the recent monographs by Jaffe (Arch. Path. **3**:414, 1927), Britton (Physiol. Rev. **10**:617, 1930) and Hartman, Brownell and Lockwood (Endocrinology **16**:521, 1932).

61. Hartman, F. A.; Aaron, A. H., and Culp, J. F.: Endocrinology **14**:438, 1930. Rowntree, L. G.; Greene, C. H.; Ball, R. G.; Swingle, W. W., and Pfiffner, J. J.: J. A. M. A. **97**:1446, 1931.

There is, however, considerable evidence of the relation of the cortex to metabolism. In earlier work, Marine and his co-workers [62a] observed that the metabolic rate of infants shows a striking increase at the time the suprarenal cortex undergoes involutional changes. At this period there is also rapid growth of the thymus and lymph glands. Marine suggested a causal relation between this normal suprarenal involution in infants and the increased heat production and lymphoid hyperplasia, particularly in view of the fact that both increased heat production and lymphoid hyperplasia may be produced in animals by sublethal injury of the cortex. The influence of the cortex in metabolism and the relation of the cortical function to disturbances of the thyroid gland and to exophthalmic goiter have been established in an extended series of experiments by Marine and his co-workers.[62] The metabolism of completely suprarenalectomized cats can be maintained by injections of the cortical hormone, according to Hartman, Griffith and Hartman [63] and Swingle, Pfiffner and Webster.[64]

The rôle of suprarenal cortex as a regulatory mechanism in the maintenance of normal conditions of temperature and muscle tone has been emphasized by Hartman and his associates,[65] Rogoff and Stewart [66] and others. Suprarenalectomized animals and patients with Addison's disease show a lowered resistance to cold. Exposure to low temperatures precipitates acute insufficiency. Suprarenalectomized rats are unable to withstand high temperatures.[67] The outstanding importance of the suprarenal tissues in the chemical regulation of body temperature was also recently emphasized and reviewed by Cannon.[68]

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62. (*a*) Marine, David; Lowe, B. H., and Cipra, Anna: J. Metab. Research **2**: 329, 1929. (*b*) Marine, David, and Baumann, E. J.: ibid. **1**:1, 1922. (*c*) Marine, David; Baumann, E. J., and Cipra, Anna: ibid. **72**:248, 1925. (*d*) Marine, David: Arch. Path. **1**:175, 1926; (*e*) Am. J. M. Sc. **180**:767, 1930. (*f*) Marine, David; Baumann, E. J., and Webster, Bruce: Proc. Soc. Exper. Biol. & Med. **28**:327, 1931. (*g*) Marine, David, and Baumann, E. J.: Am. J. Physiol. **57**:135, 1921; (*h*) **59**:353, 1922. (*i*) Shapiro, S., and Marine, David: Endocrinology **5**:699, 1921.

63. Hartman, F. A.; Griffith, F. R., and Hartman, W. E.: Am. J. Physiol. **86**:360, 1928.

64. Swingle, W. W.; Pfiffner, J. J., and Webster, Bruce: Proc. Soc. Exper. Biol. & Med. **28**:728, 1931. Webster, Bruce; Pfiffner, J. J., and Swingle, W. W.: Am. J. Physiol. **99**:710, 1932.

65. Hartman, F. A.; Brownell, K. A., and Crosby, A. A.: Am. J. Physiol. **98**:674, 1931.

66. Rogoff, J. M., and Stewart, G. N.: Am. J. Physiol. **86**:20, 1928.

67. Hartman, F. A.; Brownell, H. A., and Lockwood, J. E.: Endocrinology **16**:521, 1932.

68. Cannon, W. B.: Ergebn. d. Physiol. **27**:380, 1928.

The influence of the suprarenals on carbohydrate metabolism is primarily attributable to medullary function (Cori and Cori [69]), but the recent studies of Britton [70] indicate that in severe suprarenal cortical insufficiency of cats a low blood sugar content occurs. The concentration of the blood sugar can be raised to normal by the administration of an adequate amount of cortin (Hartman [67]).

The occurrence of a lipoid nephrosis in suprarenalectomized cats was described by Marine.[71] Marshall and Davis [72] demonstrated a steady rise in the nonprotein nitrogen of the blood in bilaterally suprarenalectomized cats. The rise in blood nitrogen is probably a terminal manifestation of a severe general disturbance in metabolism.

That the suprarenal glands are not intimately associated with cholesterol metabolism, as was believed by earlier investigators (Aschoff [5]), was demonstrated by the studies of Baumann and Holly.[73] They found no change in the blood cholesterol in suprarenalectomized rabbits except as a terminal phenomenon. The lipoid phosphorus and cholesterol show a sharp rise during the last days of life of the suprarenalectomized animal. This work has since been confirmed by Randles and Knudson [74] and by Lucas.[75]

Recent work indicates a close relationship between cortical function and cellular oxidation. In studying oxidation systems in plant life, Szent-Györgyi [76] succeeded in isolating a hexuronic acid from cabbage and other plants. He found large amounts of this strong reducing substance in the suprarenal cortex of animals, but in no other tissues does it occur in appreciable amounts.[77] From the chemical properties of this compound it is important, apparently, in oxidation-reduction systems in cellular metabolism. Independently Szent-Györgi [77] and Waugh and King [78] identified hexuronic acid with the antiscorbutic vitamin C, and King isolated the same compound from orange and lemon juice concentrates. This work opens a new field in the physiology of the suprarenal cortex in relation to the utilization of vitamin C and the importance of the cortex in certain types of anaerobic oxidation-reduction systems in

69. Cori, Carl F., and Cori, G. T.: J. Biol. Chem. **79**:309, 321 and 343, 1928.
70. Britton, S. W., and Silvette, H.: Am. J. Physiol. **99**:15, 1931.
71. Marine, David: Arch. Path. **6**:169, 1928.
72. Marshall, E. K., and Davis, D. M.: J. Pharmacol. & Exper. Therap. **8**:525, 1916.
73. Baumann, E. J., and Holly, O. M.: J. Biol. Chem. **55**:457, 1923.
74. Randles, F. S., and Knudson, Arthur: J. Biol. Chem. **67**:xvii, 1926.
75. Lucas, G. H. W.: Am. J. Physiol. **77**:114, 1926.
76. Szent-Györgyi, Albert: Biochem. J. **22**:1387, 1928.
77. Szent-Györgyi, Albert: Science **72**:125, 1930. Svirbely, J. L., and Szent-Györgyi, Albert: Biochem. J. **26**:865, 1932.
78. Waugh, W. A., and King, C. G.: Science **76**:630, 1932; J. Biol. Chem. **97**:325, 1932.

the body. (Hexuronic acid is not identical with the "life-prolonging" hormone of the suprarenal cortex.)

From this brief consideration of the physiologic action of the cortex it is apparent that the fundamental relation of the cortex to general metabolism and particularly to cellular metabolism is strongly suggested by the experimental work of many investigators.

It is the opinion of investigators in this field that the lowering of resistance is the result of an injury to all the body cells. In a recent review on this subject Marine [3] expressed the opinion that this injury is brought about by the loss or absence of some nutritional factor normally supplied by the cortex, which permits the cells of the body to be more readily attacked by various poisons.

It would seem probable that the mechanism of natural resistance is dependent on the maintenance of normal cellular metabolism and that procedures that impair oxidation and reduction processes depress the resistance of the somatic cells to all abnormal stimuli, whether marked variations in temperature or poisons, toxins or infectious agents. When the physiologic action of the cortical hormone is better understood, the chemical nature of the life-prolonging hormone identified and its relation to oxidation-reduction systems and hexuronic acid determined, a new approach to the problem of the mechanism of natural resistance in the body may be available. Natural resistance is intimately bound up with the chemistry of cellular metabolism.

SUMMARY

Removal of the suprarenal glands in rats is followed by a disturbance in the formation of antibodies, most marked during the second week after operation. The depression in antibody formation is dependent on a disturbance of the water exchange in the tissues, and restoration of a normal water exchange by the administration of large quantities of fluid containing isotonic amounts of sodium salts restores the antibody-forming capacity to normal.

The suprarenal glands are important in the maintenance of the natural resistance of the body to intoxications, poisons and bacterial and protozoan infections.

While the natural resistance of the suprarenalectomized animal is markedly depressed, the acquired resistance, produced by a previous injection of antigen or by previous infection, is unaffected.

The depression in natural resistance following suprarenal insufficiency is probaly dependent on loss of cortical function, since injections of the cortical hormone raise the resistance of suprarenalectomized animals. It is hypothecated that the depression in natural resistance is dependent on a disturbance of the general cellular metabolism, possibly of the oxidation-reduction systems.

Notes and News

University News, Promotions, Registrations, Appointments, Deaths, etc.—According to *Science* Robert Allan Moore, instructor in pathology in the Western Reserve University and assistant pathologist to Lakeside Hospital, Cleveland, has been appointed assistant professor of pathology in the Cornell University Medical College, New York.

Walter G. Sackett, bacteriologist at the Colorado Experiment Station at Fort Collins since 1908, has resigned.

John J. Phair, bacteriologist of the Cincinnati Department of Health, has been appointed to the staff of the International Health Division of the Rockefeller Foundation for work on undulant fever at Montpellier, France.

At the recent meeting of the National Tuberculosis Association in Toronto the Trudeau Medal was awarded to Lawrason Brown of the Trudeau Sanatorium, Saranac Lake, New York.

George R. Minot, of the Harvard Medical School and director of the Thorndike Memorial Laboratory in the Boston City Hospital, has been awarded the Moxon Gold Medal of the Royal College of Physicians, London, for his work on the treatment of pernicious anemia with liver.

Alan R. Moritz has been promoted to associate professor of pathology in the Western Reserve University, Cleveland.

Georges Joannovic, pathologist and founder of the Jugoslav Faculty of Medicine in Belgrade, Serbia, has died at the age of 62.

Society News.—On May 10, 1933, the American Association of Neuropathologists was established in Washington with Arthur Weil of Chicago as president and A. Ferraro of New York as secretary-treasurer.

DOCTORATES IN BACTERIOLOGY AND ANIMAL PATHOLOGY GRANTED BY AMERICAN UNIVERSITIES, 1932-1933

Clarence J. West and Callie Hull, Research Information Service, National Research Council, Washington, D. C.

BACTERIOLOGY

Chicago: Jorgen Maurice Birkeland, "Serological Studies of Plant Viruses." Mary Estill Caldwell, "Studies on Dissociation of Certain Paratyphoid Bacilli: The Rôle of Variants in the Precipitation of Calcium Sulphite." Robert Barton Dienst, "Studies on the Variation of Bacterium Dysenteriae (Sonne)."

Columbia: James Thomas Culbertson, "A Quantitative Study of the Precipitin Reaction with Special Reference to Crystalline Egg Albumin and Its Antibody." Sidney J. Klein, "The Lysis of Pneumococcus by Saponin; Sensitizing Action of Sterols." Hildrus Augustus Poindexter, "Defense Mechanism in Trypanosoma Equiperdum and Trypanosoma Lewisi Infections in Guinea-Pigs and Rats." Florence Mercedes Stone, "Porphyrin Compounds Derived from Bacteria."

Cornell: Dorsey William Bruner, "The Influence of Nutritive Conditions on Acid-Fastness of Bacteria." Fred Douglas Patterson, "Avian Coccidiosis: A Study of Some of the Factors Concerned in Its Control."

Illinois: Francis Matthew Clark, "The Formation of Hydrogen Sulfide by Thermophilic Bacteria." John B. Rehm, "The Effect of Aeration on Micro-Organisms." Elbert Hollis Ruyle, "The Microbiology of Canned Meat Products." Isaac Evan Wheaton, "The Effect of Salt on Micro-Organisms."

Iowa State College: Mervyn Avery Collins, "The Action of Lipolytic Bacteria on Some Simple Tri-Glycerides and Some Natural Fats." Arthur Cecil Fay, "The Effect of Hypertonic Sugar Solutions on the Thermal Resistance of Bacteria." William Hillman Willis, "The Metabolism of Some Nitrogen-Fixing Clostridia."

Johns Hopkins: Andrés Rodríguez, "The Survival of Members of the Bacillus Coli-Lactis Aerogenes Group in Milk Pasteurized in the Laboratory and in the Commercial Plants, with Observations on the Resistance of Bacillus Coli to a Temperature of 142 F."

Kansas: Mary Elizabeth Elmore, "A Further Study of the Antigenic Properties of Euglena Gracilis, Klebs, with Related Phenomena." Paul W. Kabler, "Studies in Anaphylaxis."

Michigan: Ardzroony Arthur Packchanian, "Experimental Trypanosoma Brucei Infection and Immunity in Various Species of Animals; Blood Chemistry and Electrical Conductivity of Nagana Blood."

Minnesota: William Richard Carroll, "A Study of Rhizobium Species in Relation to Nodule Formation on the Roots of Florida Legumes." Ernest Oliver Herreid, "The Microbiology of Cheeselike Flavors in Unsalted Butter."

New York: Dorothy Behner Holmes, "Studies in the Virulence and Colony Variability of Tubercle Bacilli Developed Under Different Conditions with Especial Reference to the Bacillus Calmette-Guérin."

Northwestern: Arnold Gerhard Wedum, "Investigation of Certain Synthetic Glucosides for Antigenic Properties."

Ohio State: Ruth Ella Moore, "I. Studies on Dissociation of Mycobacterium Tuberculosis: II. A New Method of Concentration of the Tubercle Bacilli as Applied to Sputum and Urine Examination."

Pennsylvania: Albert Dickman, "Studies on the Waxmoth, Galleria Mellonella, with Particular Reference to the Digestion of Wax by the Larvae."

Rochester: Ralph Porter Tittsler, "The Electrophoresis of Escherichia Coli Grown on Culture Media of Varied Composition."

Rutgers: Ernest Rudolph Purvis, "A Study of Microbiological Population of Peat and Its Rôle in the Chemical Processes of Peat Formation."

Virginia: Leland Edson Starr, "Undulant Fever and Its Relation to Brucelliasis in Cattle and Swine in Virginia."

Wisconsin: Lawrence Wayneworth Brown, "The Relation of the Oxidation-Reduction Character of Sterile Bacteriological Media to the Growth of Aerobic Organisms." Janet Ruth McCarter, "The Bacteriology of Certain Species of Micro-Organisms, Both Those Belonging in and Those Related to the Genus Mycobacterium." Marion Henrietta Thauer, "Certain Factors Affecting the Reduction of Methylene Blue in Milk."

Yale: George Dexter Brigham, "A Systematic Study of the Pasteurella Genus." Ruth Cameron, "A Search for a Specific Toxin in Salmonella Aertrycke (Var. Meleagridis)." Stanley Eugene Hartsell, "The Taxonomy of Clostridium Putrificum and Its Establishment as a Definite Entity: Clostridium Lentoputrescens, Nov. Spec." James Ewing Weiss, "Lactobacillus Bifidus Tissier and Its Biological Position in the Group of Aciduric Organisms."

ANIMAL PATHOLOGY

Johns Hopkins: John Holmes Dingle, "Bacterial Carbohydrates: Their Isolation, Serological Specificity and Immunological Significance." Aurel Overton Foster, "Studies on the Resistance of Dogs and Cats to Infection with the Dog Hookworm, Ankylostoma Canium." Vernal Irons, "Studies on Bird-Pox (Epithelioma Contagiosum)." Sydney Raffel, "Specific and Nonspecific Immunity in Trypanosoma Equiperdum Infections." Mary Shaw Shorb, "Heterophile Antigen in Bacteria."

Abstracts from Current Literature

Experimental Pathology and Pathologic Physiology

EXPERIMENTAL FAT EMBOLISM OF THE HEART. S. A. SZUREK and Z. G. CZAJA, Am. J. Path. **9**:47, 1933.

From 1 to 2 cc. of oil squeezed from the omental and subcutaneous fat of normal dogs was injected into the descending branches of the anterior coronary artery of dogs. The heart was examined at various subsequent periods for thirty days. In limited portions of the myocardium blocking of all the capillaries with oil appeared to be followed by infarction rather than by the occlusion of the arterial branches which occurs in ordinary coronary thrombosis and embolism. Muscular fibers adjacent to oil infarcts were fatty at times, but it could not be decided whether the fat in such fibers was embolic in origin and had accumulated in the fiber after passing through the capillary wall. It is concluded that fat embolism should be considered as a possible cause of minute scars scattered through the myocardium.

THE EFFECTS OF POTASSIUM BICHROMATE ON THE MONKEY'S KIDNEY. W. C. HUNTER and J. M. ROBERTS, Am. J. Path. **9**:133, 1933.

Potassium bichromate in dosages employed in experiments performed on monkeys affects diffusely the proximal and distal convoluted tubules and glomeruli of the kidney. The type of injury is comparable to that induced by uranium nitrate and mild mercurous chloride. The drug is locally corrosive when administered subcutaneously, and the quantity absorbed varies considerably in different animals of the same species. Definitely chronic renal lesions were obtained in but one animal of six. Following repeated injections of potassium bichromate there occurs a regeneration of tubular epithelium of distinctly atypical morphology which is resistant to further injury by the nephrotoxin. AUTHORS' SUMMARY.

MYCOSIS FUNGOIDES IN MOTHER AND IN DAUGHTER. OLIN J. CAMERON, Arch. Dermat. & Syph. **27**:232, 1933.

A woman, aged 45, had mycosis fungoides which resulted fatally four years later. Five years after her death her daughter, aged 28, presented the typical picture of mycosis fungoides. This is the first instance of mycosis fungoides reported in two members of the same family, although the familial occurrence of leukemia and of Hodgkin's disease has been reported. S. W. BECKER.

SIMMONDS' DISEASE (CACHEXIA HYPOPHYSEOPRIVA). SOLOMON SILVER, Arch. Int. Med. **51**:175, 1933.

Simmonds' disease may be defined as a clinical state, occurring most commonly in women and characterized by progressive, extreme emaciation, premature aging, wrinkling of the facial skin, loss of pubic and axillary hair, dental caries and loss of libido and sexual function, accompanied by a depression of the basal metabolic rate and, often, by mental disturbances closely simulating Korsakoff's syndrome. In addition to advanced obvious cases, attention is called to the mild, abortive forms that masquerade under such diagnoses as arteriosclerotic cachexia, syphilitic cachexia and latent tuberculosis. The pathologic basis for the condition is varied, but in general may be stated as any process resulting in the destruction of the anterior lobe of the pituitary gland. The only constant postmortem observation is an abnormal smallness of the viscera, which was first pointed out by Simmonds. Since it is now established that acromegaly depends on the hyper-

activity of the eosinophilic elements, it is perhaps not unlikely that Simmonds' disease has as its physiologic basis a hypofunction of these cells. At least one might expect something of this nature from the directly opposite clinical pictures presented by acromegaly and by Simmonds' disease. It is noted, however, that extensive, almost complete destruction can take place without evidence of characteristic symptoms.

IRVING B. GOLD.

INFLUENCE OF THE PITUITARY GLAND ON ERYTHROCYTE FORMATION. R. C. MOEHLIG and G. S. BATES, Arch. Int. Med. **51**:207, 1933.

Two cases of polycythemia vera with pituitary basophilism, which came to autopsy, are described. One was a case of primary basophilic adenoma giving rise to the syndrome recently described by Cushing. The other was a case of secondary basophilism in response to a suprarenal tumor. The occurrence of polycythemia experimentally induced in dogs by bilateral adrenalectomy is also reported. In these animals rapid and marked hyperplastic changes of the pituitary cells were found. The hyperplasia was, in the majority of cases, confined to the basophil cells. The pituitary secretion has an important influence on erythrocyte formation. Primary disease of the suprarenal cortex results in secondary pituitary changes, and this accounts for many signs and symptoms erroneously ascribed to the suprarenal cortex. The specific and selective embryohormonic relations of the pituitary gland to mesodermal tissues offer a reasonable explanation for the polymorphic signs and symptoms of pituitary disturbances.

AUTHORS' SUMMARY.

ACIDS AND OTHER SUBSTANCES IN THE PRODUCTION OF GASTRIC ULCERS. J. FRIEDENWALD, M. FELDMAN and S. MORRISON, J. Exper. Med. **57**:203, 1933.

The various substances utilized in these experiments, when injected into the muscular coat of the wall of the stomach, did not have any significant relationship to the production of ulcer. Weak solutions of hydrochloric acid had no corrosive effect on the gastric mucosa and rarely produced ulceration. Stronger solutions produced definite ulcerations. No relationship could be demonstrated between the injection of various substances into the stomach wall and the production of hyperacidity. The prolonged use of histamine administered subcutaneously was not a factor in the production of chronic ulcers, even after a 1 per cent solution of hydrochloric acid was injected into the muscular coat of the stomach.

AUTHORS' SUMMARY.

EFFECTS OF ANTERIOR PITUITARY EXTRACTS ON METABOLISM. O. H. GAEBLER, J. Exper. Med. **57**:349, 1933.

Solutions of the globulin fraction of alkaline extracts of the anterior lobe of beef pituitary glands, when administered intraperitoneally or subcutaneously to dogs for one or two days, greatly increase the nitrogen balance. The nitrogen content of the urine falls markedly and the nonprotein nitrogen of the blood decreases, while the nitrogen of the feces remains the same. The nitrogen gained may be either retained or lost, indicating that it may be converted into reserve protein rather than into permanent structures. Sudden gains in weight which follow the injections are always followed by losses in weight. The effect of the extracts on protein catabolism is greatest when the latter is high, as in adult dogs having either a negligible positive nitrogen balance or a negative nitrogen balance, while consuming a diet high in protein and adequate in calories. Both the fall and the subsequent rise in the excretion of nitrogen are due to changes in the excretion of urea. Other results of the brief treatments are: great increase in the intake of water and in the volume of urine, marked thirst, a slight rise in temperature and a remarkable increase in heat production effected by the oxidation of fat. Mature female dogs were used, and in one of these lactation occurred after some of the injections.

AUTHOR'S SUMMARY.

NUTRITIONAL ENCEPHALOMALACIA IN CHICKS. A. M. PAPPENHEIMER and M. GOETTSCH, J. Exper. Med. **57**:365, 1933.

Nutritional encephalomalacia may be induced in chicks up to the age of approximately 2 months. As the number of preliminary feeding periods of a natural diet is increased, the percentage incidence of the disease becomes progressively less. The average time between the institution of the diet and the appearance of the disease tends to diminish. There is no correlation between growth and incidence of the disease. Various breeds are equally susceptible.

AUTHORS' SUMMARY.

EFFECT OF E AVITAMINOSIS ON THE INTERSTITIAL CELLS OF THE TESTIS. A. JUHÁSZ-SCHÄFFER, Virchows Arch. f. path. Anat. **286**:834, 1932.

Opinions as to the function of the interstitial cells of the testis have been based to a large degree on procedures that lead to atrophy and disappearance of the tubular epithelium. More recent opinion tends to the conclusion that the increase in interstitial tissue that follows such procedures is apparent rather than real. In a previous communication the author described the effects of a deficiency of vitamin E on the testis of young rats. Spermatogenesis ceases, the seminal tubular epithelium degenerates and disappears, and the testis becomes atrophic. The interstitial tissue not only is unchanged but appears relatively more prominent than normal. The aim of the present investigation was to determine whether any actual changes in the amount of the interstitial tissue occur. Planimetric methods of determining the relative volumes of interstitial tissue and tubular tissue in relation to the entire testis proved unsatisfactory. The method finally selected was the counting of the nuclei of the interstitial cells of the testes of rats on a diet deficient in vitamin E and of their normal litter mate controls. No significant change in the number of interstitial cells could be detected. Similar negative results were obtained when a unilateral castration was done before the rats were placed on the deficient diet. During the period of recovery from the changes induced by the deficient diet, in which regeneration of the tubular epithelium occurs, no changes in the number of interstitial cells were noted.

O. T. SCHULTZ.

ALCOHOL AND CIRRHOSIS OF THE LIVER. RUDOLPH SIVO, ELEMER EGEDY and JOSEF ERDOS, Ztschr. f. d. ges. exper. Med. **84**:459, 1932.

In healthy persons the albumin-globulin ratio varies between 3.0 and 5.5, the average being 3.9. The globulin value varies from 15 to 24 per cent. This ratio remains constant under all sorts of physiologic conditions of the organism. In cirrhosis of the liver there is a significant increase in globulin at the expense of the albumin, the albumin-globulin ratio averaging 0.96 and ranging from 1.8 to 0.49, but the diagnosis of hepatic cirrhosis cannot be determined on this basis alone. In alcoholic patients who do not have cirrhosis of the liver the albumin-globulin ratio is around 2.01, and this increase in globulin denotes a disposition to cirrhosis. In animal and human experiments occasional ingestion of alcohol leads to a temporary increase in globulin, and with the persistent use of this substance the globulin increase becomes established. Tuberculosis and syphilis of long duration also lead to an increase in globulin as do other factors concerned in the etiology of cirrhosis of the liver.

AUTHORS' SUMMARY.

THE ORIGIN OF CREATINE AND THE TREATMENT OF PROGRESSIVE MUSCULAR ATROPHIES WITH GLYCINE. KARL THOMAS, ADE T. MILHORAT and FRITZ TECHNER, Ztschr. f. physiol. Chem. **205**:93, 1932.

Patients with progressive muscular atrophy were fed glycine, and an increased creatinuria was observed, which gradually decreased and sometimes reached values below those present before the onset of treatment. During the stage of hypercreatinuria the patients complained of pain and an itching sensation in the muscles, especially the last affected ones. These symptoms disappeared gradually with the

decrease of the creatine excretion. The patients felt less tired and were able to use their muscles. The improvement lasted for about one month after discontinuation of the treatment. Patients with secondary muscular atrophy (amyotrophic lateral sclerosis, rheumatic arthritis, congenital idiocy) did not respond to treatment with glycine. It is asserted that the administration of glycine represents a causative therapy in progressive muscular atrophy. WILHELM C. HUEPER.

Pathologic Anatomy

CEREBRAL ANEURYSMS AS SOURCES OF APOPLECTIC HEMORRHAGES. H. BEITZKE, Beitr. z. path. Anat. u. z. allg. Path. **87**:272, 1931.

Twelve cases of cerebral hemorrhage were studied for aneurysms by serial sections, and aneurysms were found in seven. The aneurysms were small (from the size of a grain of sand to that of a millet seed). In six cases the histologic picture was that of atherosclerosis (termed angionecrosis by some authors). There is considered to be a primary focal medial injury. If this is gradual, dilatation and compensatory intimal thickening occur; if it is acute, necrosis or calcification of the media occurs, there is no compensatory internal change, and an aneurysm forms rapidly. Syphilis was found in one case.

The author believes cerebral aneurysms more frequent in the pathogenesis of hemorrhage than reports would indicate. The cause of the medial injury he regards as either sclerosis or syphilis. The rupture is produced by sudden rises in tension. The occurrence of a huge hemorrhage as the result of the conglomeration of multiple small hemorrhages is considered rare. W. S. BOIKAN.

SILICOSIS OF THE SPLEEN. A. EDINGER, Centralbl. f. allg. Path. u. path. Anat. **55**:1, 1932.

A firm spleen, 17 by 9.5 by 3.5 cm., containing many nodules and firm yellow streaks in the pulp, was found in the body of a 36 year old woman who had suffered from chronic mitral endocarditis and glomerular nephritis and who died of uremia. The nodules consisted of concentric layers of connective tissue in the wall of thickened blood vessels and in the smaller trabeculae. Similar nodules occurred in the lung parenchyma, in the walls of the bronchi and pulmonary vessels, in the lymph glands of the hili of the lung and spleen and in the posterior mediastinum. In the nodules quartz dust was found, although in all of them it appeared that silicon dioxide had induced a connective tissue reaction much greater than that occasioned by the infiltration of dust alone. Edinger believes that the transport of silicates may have occurred either through the blood stream after intravasation in the pulmonary lymph glands or in a retrograde fashion through the lymph channels into the spleen.

GEORGE RUKSTINAT.

RELATION BETWEEN THE SIZE AND WEIGHT OF THE SPLEEN. E. VON GIERKE, Centralbl. f. allg. Path. u. path. Anat. **55**:129, 1932.

The author believes that a rather accurate idea of the weight of the spleen can be obtained by expressing as weight in grams one-half the product of the length, breadth and thickness in centimeters. He cites examples in which exact weights and measurements seem roughly to substantiate his ideas.

GEORGE RUKSTINAT.

UNUSUAL LIPOMATOSIS OF THE PANCREAS. O. MICHAELIS, Centralbl. f. allg. Path. u. path. Anat. **55**:131, 1932.

The pancreas was so large that it could be palpated through the abdominal wall and was thought to be a malignant tumor. A large, knobbed, fist-sized portion of the organ reached the hilus of the liver, surrounded the vessels here and compressed the portal vein and cisterna chyli. The tail of the tumor was the size of

a child's arm, and was intimately connected with the surrounding tissues. A chylous ascites of 3.5 liters existed. The fat in the pancreas was predominantly cholesterol, and in it small and large clumps of pancreas were visible microscopically. The origin of this huge fatty deposit apparently lay in the lipoid nephrosis from which the patient had suffered.

GEORGE RUKSTINAT.

CHANGES IN THE CARTILAGE OF AN ANKYLOSED KNEE JOINT. A. L. ROSI, Virchows Arch. f. path. Anat. **284**:256, 1932.

The structure of a joint is the result of static and mechanical factors, and the relations of bone, cartilage and connective tissue are such as best adapt the joint to the dynamics of its function. Ankylosis sets aside the normal functions of a joint, while weight-bearing and locomotion subject the ankylosed joint to mechanical factors different from those that are operative in the normal joint. Roux made a gross study of the changes in the bones of an ankylosed knee joint. Rosi presents a histologic study of tissues of an ankylosed knee-joint. The ankylosis had occurred in early childhood, when developmental changes were still in progress in the structures of the knee. Tuberculosis of the joint at the age of 2 years had been followed by healing with preservation of some of the cartilaginous structures and by bony ankylosis of the joint in the flexed position. The child died at the age of 13½ years. During the period of inactivity, partial resorption of the persisting cartilage had occurred. When the joint was again subjected to mechanical stress and strain, proliferation of cartilage filled the defects with new-formed cartilage. The older cartilage underwent asbestos-like degeneration of its matrix, and where subjected to greatest stress, the cartilage had been replaced by fibrous tissue. Microfractures of bone and calcified cartilage occurred at points of greatest stress. The fatty marrow of the enlarged spaces of the original bone was supported by fine trabeculae of new-formed bone. Fixation of the joint in flexion had led to shifting of the insertion of the patellar ligament into the patella.

O. T. SCHULTZ.

HISTOGENESIS OF MESOGLIA. W. K. BELEZKY, Virchows Arch. f. path. Anat. **284**:295, 1932.

The origin and histogenesis of the mesodermal glial constituents of the central nervous system were studied in the chick and rabbit embryo and in new-born kittens. In the chick, on the fourth day of embryonic development, histiocytes can be recognized in the mesenchyme about the central nervous system. The histiocytes penetrate the nervous system with the choroidal and pial vessels. Within the nervous system, during further development, they become transformed into various types of cells, the character of which depends on their location and function. In the subependymal tissue and in the deeper white matter, they become drainage cells, which have no processes and bear a relation to tissue spaces and lymphatics. In the deeper layer of the cortex, they are transformed into oligodendroglia, and in the middle and superficial layers of the cortex, into Hortega cells, the function of which is the adsorption of materials from the cerebrospinal fluid. In the cortex, the processes of the cells are in contact with each other, but do not form a syncytium. The various cells of the mesoglia constitute a system of reticulo-endothelial origin. They retain the functional potencies of the reticulo-endothelial system and may manifest these functions in pathologic states. The glia of mesodermal origin, consisting of drainage cells, oligodendroglia and Hortega cells, may be termed the microglia, in contradistinction to the glia of ectodermal origin, or macroglia, composed of astrocytes.

O. T. SCHULTZ.

HISTOLOGY OF BALANTIDIUM COLITIS. H. HARMS, Virchows Arch. f. path. Anat. **284**:422, 1932.

In the case of Balantidium colitis that Harms had the opportunity to examine post mortem, there were multiple small ulcers in the colon. Some of the ulcers

were fresh, others were clean ulcers, and still others were in process of healing. In the earliest ulcers, it could be seen that the protozoa entered the crypts of the mucosa and penetrated between the epithelial cells. In the tissue of the mucosa they caused an inflammatory reaction that led to necrosis and to destruction of the overlying mucosa. The organisms did not penetrate the intact muscularis mucosae. Involvement of the submucosa developed when penetration occurred at the solitary follicles or by way of the capillaries or through areas of necrosis. The organisms apparently entered the capillaries readily, but were killed in the blood stream.

O. T. SCHULTZ.

BILATERAL GRANULOSA CELL TUMOR OF THE OVARIES WITH METASTASIS TO BONE. C. H. SOLTMANN, Virchows Arch. f. path. Anat. **284**:466, 1932.

Tumors of the ovary derived from the granulosa cells of the follicles are not uncommon, but metastasis of such tumors has been infrequently reported. The tumor described by Soltmann was bilateral and occurred in a woman aged 43. Death on the tenth day after operation was due to paralytic ileus. The primary tumors were diffusely cellular. They contained folliculoid areas and columnar cell adenomatous fields. At necropsy, metastases were found in the sacrum. The folliculoid character of the tumor was much more evident in the metastases than in the primary tumor.

O. T. SCHULTZ.

GIANT CELLS IN AN APPENDIX REMOVED DURING THE INCUBATION PERIOD OF MEASLES. W. FINKELDEY, Virchows Arch. f. path. Anat. **284**:518, 1932.

In a previous article (**281**:323, 1931), abstracted in the ARCHIVES, the author reported the presence of giant cells of peculiar type in tonsils that had been removed during the period of incubation of measles. In the present article, he describes similar giant cells in an acutely inflamed, ulcerated appendix removed two days before the eruption of measles appeared, in a boy, aged 8. Finkeldey considers the giant cells of the lymphoid tissue of the tonsils and appendix a specific allergic reaction to the toxin of measles.

O. T. SCHULTZ.

THROMBO-ANGIITIS OBLITERANS. E. JÄGER, Virchows Arch. f. path. Anat. **284**: 526 and 584, 1932.

In two consecutive communications, ninety-four pages, Jäger gives an excellent and richly illustrated study of thrombo-angiitis obliterans, which since the time of Billroth and von Winiwärter has usually been referred to in the German literature as juvenile spontaneous gangrene. The study is based on four cases completely examined at necropsy and amputation material from twelve additional cases. A fifth case, in which necropsy was done, was included at the time of correction of proof, but does not receive so full a discussion. He also tabulates seven previously recorded cases that were examined post mortem. The earliest and what Jäger considers the most essential lesion of the disease is localized fibrinoid degeneration of the superficial part of the intima of the larger arteries. This leads to localized reactive cellular proliferation of the intima, which may be almost polypoid, and which leads to narrowing of the lumen. Such lesions are multiple and are found not only in the femoral artery and its branches, but also in the aorta, the coronary arteries, the circle of Willis and the arteries of the internal organs. The differences between the intimal lesions of thrombo-angiitis obliterans and those of arteriosclerosis are fully described and discussed, as are those of the early fibrinoid degenerative stage of acute rheumatic infection. The intimal involvement leads to red thrombosis. The latter process does not begin in the terminal vessels and propagate itself centrifugally, but occurs at the sites of intimal involvement of the larger arteries. The canalized tissue, which fills the larger arteries and which is a striking histologic feature of the later stages of the disease, is the result of organization of thrombi and not of inflammation

in the narrower sense. The intima peripheral to the areas of occlusion proliferates diffusely. This is a compensatory process, and is likewise noninflammatory. An active proliferative inflammatory reaction occurs in the terminal arteries and veins; the differentiation of this lesion from periarteritis nodosa is discussed. Occlusion of the larger veins is due to stasis thrombosis; this is followed by organization with canalization. Canalization of the venous thrombi may be adequate for return circulation; in the arteries it does not help to reestablish circulation. Healing of the intimal lesions of the larger arteries may occur, with the formation of areas of arteriosclerotic atheroma. In the early proliferative stage of the intimal lesions, giant cells, sometimes of Langhans' type, may be formed. Gangrene of the lower extremities need not be a feature of the disease. It is a late manifestation of a process that involves the arterial system widely. The disease, in Jäger's opinion, is a characteristic or specific vascular reaction, possibly on a constitutional basis, to a variety of causative agents. For this disease, he accepts thrombo-angiitis obliterans as the best designation. In the discussion and in the four closely printed pages of references due attention is given to the important American literature on the subject. O. T. SCHULTZ.

TONSILLAR CHANGES IN RHEUMATIC FEVER. F. KLINGE, Virchows Arch. f. path. Anat. **286**:333, 1932.

The tissue reactions that Klinge has described as characteristic of rheumatic infection occur in collagenous connective tissue. Such changes are therefore not to be expected in the reticulo-endothelioid lymphoid tissue of the tonsil itself. But in necropsy material rheumatic lesions have been observed in the peritonsillar tissues. Examination of tonsils removed during the acute or subacute stage of rheumatic fever has yielded inconstant results. In two pairs of such tonsils examined by Klinge there were numerous rheumatic lesions of the peritonsillar tissue, and in a third pair there were a few lesions, but in other tonsils the findings were negative. The results of examination of tonsils removed during a first or recurrent attack of rheumatic fever, taken in connection with the results of Sarafoff's examination of tonsils and tissues of the neck at necropsy, warrant the assumption that the rheumatic virus may enter the body through any part of the upper respiratory tract as well as through the tonsils. O. T. SCHULTZ.

PATHOLOGIC ANATOMY OF BRONCHIAL ASTHMA. W. PAGEL, Virchows Arch. f. path. Anat. **286**:580, 1932.

A man, aged 30, who had been subject to bronchial asthma for years, died suddenly in a paroxysm, evidently as the result of bronchial spasm. The changes that were noted in the bronchi and that Pagel considers characteristic of asthma were the presence of mucous spirals with crystals and eosinophils in the bronchial lumen, eosinophilous infiltration of the epithelium, plateau-like elevations and hernia-like depressions of the epithelium, thickening of the basement membrane, atrophy of the muscularis mucosae and hypertrophy of the smooth muscle of the submucosa. The mucus within the lumen of the bronchus comes in part from the mucous glands of the wall and in part from mucous degeneration of the epithelium. The plateau-like elevation of the epithelium is due to localized thickening of the elastic fibrils of the internal limiting membrane, and this in turn is compensatory to atrophy of the muscle fibers of the muscularis mucosae.

O. T. SCHULTZ.

MILIARY TUBERCLES IN THE SKIN IN MILIARY TUBERCULOSIS. P. GEIPEL, Virchows Arch. f. path. Anat. **286**:591, 1932.

To three previously recorded cases of generalized miliary tuberculosis in which he found tubercles in the skin, the author adds two similar cases. The tubercles

were situated either deeply or superficially in the corium; when they are superficial the epidermis may also be involved. All the cases were in nurslings. Geipel has never seen tubercles in the skin in miliary tuberculosis in adults. The subcutaneous tissue, on the other hand, practically uniformly reveals the presence of tubercles in miliary tuberculosis at all age periods.

O. T. SCHULTZ.

EFFECT OF TUBERCULOTOXIN ON THE LIVER. H. GUILLERY, Virchows Arch. f. path. Anat. **286**:605, 1932.

Previous work of the author, in which he ascribed the formation of tuberculoid granulomatous lesions and small areas of necrosis in the liver to the distant action of toxins derived from collodion sacs containing viable tubercle bacilli that had been implanted in the peritoneal cavity of rabbits, has been criticized. Some of his critics have obtained negative results by a similar method of procedure, and still others have ascribed the lesions to the action of bacilli rather than of their toxins. In the present series of experiments, Guillery used the phosphatide isolated from human tubercle bacilli by R. J. Anderson of the Rockefeller Institute. Eighty milligrams of the material in 10 cc. of distilled water was injected daily into rabbits intravenously. Each animal received from twelve to twenty injections and was killed at the end of the series of injections. In the liver there were found cellular lesions similar to those previously described. Necrosis did not occur. There was noted also the formation of Langhans' giant cells surrounded by normal liver cells, with no cellular infiltration. The author considers that the giant cells are derived from reticulo-endothelial elements that react as the result of their detoxifying function.

O. T. SCHULTZ.

CHANGES IN THE HYPOPHYSIS ASSOCIATED WITH ALTERATIONS IN THE MIDBRAIN. E. J. KRAUS, Virchows Arch. f. path. Anat. **286**:656, 1932.

Increased intracranial pressure is frequently associated with enlargement of the hypophysis, the enlargement being due to an increase in the size of the anterior lobe. The hypertrophy of the anterior lobe is due to hypertrophy and hyperplasia of its constituent cells, especially the eosinophil cells. It is requisite for the hypertrophy that the increased intracranial pressure is of sufficient duration and that the connection of the hypophysis with the midbrain is not disturbed. If the increased pressure is due to a condition that has caused destruction of the base of the midbrain or to a lesion of the stalk that separates the hypophysis from the midbrain, the anterior lobe undergoes atrophy rather than hypertrophy. The eosinophil cells are decreased in size and number. Kraus briefly describes twelve examples of atrophy associated with lesions of the midbrain or stalk. In one of these, which was a case of congenital dwarfism, separation of the hypophysis from the midbrain and failure of complete union of the anterior and posterior lobes, with resulting atrophy of the anterior lobe, were believed to be the result of congenital maldevelopment. From the study of these cases and of a much larger group in which intracranial pressure was associated with hypertrophy of the anterior lobe, Kraus concludes that lesions of the midbrain or hypophyseal stalk interfere with the liberation of the anterior lobe hormone and lead to atrophy of the anterior lobe. The condition of the gonads in cerebropituitary disease depends on the functional activity of the anterior lobe of the hypophysis and on the degree to which involvement of the midbrain interferes with the liberation of the hormone. The hypertrichosis of cerebropituitary disease may be the result of changes in the anterior lobe of the hypophysis or of changes in the gonads or of both combined. The obesity of cerebropituitary disease results from destruction or involvement of centers in the midbrain. The diminished function of the anterior lobe of the hypophysis resulting from such lesions of the midbrain may later lead to a decrease in, or disappearance of, the obesity.

O. T. SCHULTZ.

RECURRENT VENOUS THROMBOSIS OF INTERNAL ORGANS IN A CASE OF SUBACUTE SEPSIS. J. CATSARAS and A. SYMEONIDIS, Virchows Arch. f. path. Anat. **286**:733, 1933.

In a man, aged 42, an attack of grippal bronchopneumonia of fifteen days' duration was followed by thrombosis of the right and left femoral veins. Then there occurred severe pain in the region of the left kidney. Still later a severe attack of abdominal pain led to laparotomy and resection of the infarcted omentum. The various attacks were ushered in by chills and fever, and were accompanied by leukocytosis. Death occurred four and a half months after the onset of the illness. Thrombi of variable age and in various stages of organization were found in the pulmonary, portal, splanchnic, renal and splenic veins. Postmortem cultures of the heart's blood remained sterile, but the condition is ascribed to pneumococcic sepsis.

O. T. SCHULTZ.

CHRONIC OCCLUSION OF THE PORTAL VEIN. H. FLEISCHHAUER, Virchows Arch. f. path. Anat. **286**:747, 1932.

The author briefly reviews the previously reported cases of chronic occlusion of the portal vein, a condition which he contrasts with the sudden thrombosis of the portal and mesenteric veins that leads quickly to death by intestinal infarction. He presents two cases of his own, each in a man aged 52. In each case death was due to hemorrhage from esophageal varices. In the first case occlusion of the portal vein by an organized thrombus was consecutive to phlebosclerosis and thrombosis of the mesenteric and splenic veins, a process which, in its turn, is ascribed to a previous attack of appendicitis. A collateral circulation had been formed by way of the coronary and pyloric veins of the stomach. In the second case the organized thrombus of the portal vein was associated with an angiomatous plexus of veins at the hilus of the liver. For the explanation of this case the author subscribes to the view of Pick, that occlusion or obliteration of the portal vein and the associated cavernous hemangioma of the hilus of the liver are the result of embryonic maldevelopment.

O. T. SCHULTZ.

VASCULARITY OF THE PERIOSTEUM. H. NAUMER, Virchows Arch. f. path. Anat. **286**:766, 1932.

The cambium layer of the normal periosteum is described as having few blood vessels. When acutely inflamed, it is highly vascularized. The author injected turpentine into or beneath the periosteum of the femur and humerus of guinea-pigs and studied the tissue histologically at intervals of from six hours to twelve days. The cambium layer contained many engorged capillaries that were continuous with those of the haversian canals. The high degree of vascularity, as early as six hours after injection of the irritant, is interpreted as proof of the presence of numerous collapsed capillaries in the normal periosteum.

O. T. SCHULTZ.

THE NATURE OF ARGENTAFFIN CELLS. H. HAMPERL, Virchows Arch. f. path. Anat. **286**:811, 1932.

This is a critical survey of the technical methods used for the silver impregnation of tissues and of the conclusions to be drawn from the results of the application of such procedures. The discussion is limited to the impregnation of cells, and leaves out of consideration the impregnation of fibers, fibrils and intercellular substances. The varieties of cells that may be impregnated with silver depend on the method used. It is therefore meaningless to refer to a cell type as "argentaffin" unless the method used in bringing about the silver reaction is specified. Any single method may yield variable results if slight variations in technic are introduced. It is unwarranted to group together as an "argentaffin system" the various types of cells that may give a positive silver reaction, or to

base an assumption of the affinity of two or more cell types on the outcome of the silver impregnation technic alone. The author closes his article with a quotation from Goethe to the effect that it is much more important, in attempting to obtain a true knowledge of things, to note in what respects they differ than in what respects they may be identical. One is inclined to agree that this philosophy of Goethe's is still a good safeguard against the drawing of hasty conclusions based wholly on the outcome of a technical procedure.

O. T. SCHULTZ.

OCCURRENCE OF FATTY SUBSTANCES IN THE SPUTUM AND IN THE LUNGS. U. QUENSEL, Festschrift, Upsala läkaref. förh., 1932, vol. 38, article 15.

Quensel points out that until recent years the function of the lung was considered only as far as it is concerned with the gas exchange of the organism. However, recent researches have revealed that in the pulmonary tissues various other processes, such as storage, digestion, resorption, filtration and elimination, take place. This report, however, is concerned only with the rôle of the lung in fat metabolism. For the cytologic examination of the sputums Quensel found staining with his solutions of methylene blue (methylthionine chloride, U. S. P.) and sudan or cresyl violet helpful. This method of staining is also suitable for unfixed frozen sections of lung tissue. In order to be able to study the position of the various cell elements in the mucus of the sputum it is advisable to fix the sputum globules in Bouin's fluid, embed them in paraffin and then stain the sections in the usual manner. To determine the occurrence of fat substances in the lungs the examination of unfixed frozen sections is best, and this method can also be used for sputums. In the sputums of healthy persons large cells can be demonstrated regularly, which may be considered as eliminated alveolar epithelial cells. They occur in various forms, with or without inclosures, and are identical with the so-called alveolar phagocytes. Quite frequently they are more or less laden with fatty substances, which for the largest part prove to be anisotropic. In addition to this, free fat is found in every sputum, generally the so-called myelin forms. In normal lung tissues fat substances of the same appearance and of the same type as those in the sputums are found regularly. The fat substances in the sputum apparently originate in the pulmonary tissues, where they occur either free or in the alveolar phagocytes. The sputum of patients with pulmonary tuberculosis contains, as the sign of an inflammatory process, a larger or smaller number of polymorphonuclear leukocytes. In addition to these, large cells of the same type as the alveolar phagocytes or the alveolar epithelium in the normal sputum are demonstrable. Their number increases as the sputum takes on the appearance of the normal sputum. Here again the large cells are more or less laden with fat that for the most part is also anisotropic. In view of the regular occurrence of fat substances in the normal sputum and lung, it seems likely that the fat-containing cells which are found in pulmonary tuberculosis originate in the healthy portions of the lung, and thus are not indicative of a pathologic process. All these observations seem to indicate that normally the lungs participate in some manner in the fat metabolism of the organism, because on the one hand there is an accumulation of fats in the lungs and on the other hand an elimination.

Pathologic Chemistry and Physics

UNIVERSAL CALCINOSIS. B. J. HEIN, Arch. Surg. **26**:389, 1933.

A girl, aged 6½ years, had diffuse deposits of calcium salts in the fasciae (universal calcinosis). The deposits diminished and improvement occurred with heliotherapy. The calcium salts apparently were removed by giant cell reactions, preceded by a granular disintegration of the masses. The patient has been under observation for four years.

EDWIN F. HIRSCH.

ENHANCED LETHAL EFFECTS OF X-RAYS ON BACILLUS COLI IN THE PRESENCE OF INORGANIC SALTS. W. D. CLAUS, J. Exper. Med. **57**:335, 1933.

When B. coli are irradiated by the x-rays in a series of salt solutions of tenth-molar concentration, the synergistic effect does not become appreciable until heavy salts are used.

FROM AUTHOR'S SUMMARY.

EXOGENOUS AND ENDOGENOUS IRON PIGMENT IN THE LUNGS. K. F. SCHEID, Beitr. z. path. Anat. u. z. allg. Path. **88**:224, 1932.

Lungs of iron miners were examined histochemically. The incineration method of Schultz-Brauns was helpful. In the pulmonary tissue the inhaled ferrous carbonate is changed into a pigment which, by histochemical methods, cannot be differentiated from hemosiderin. The same pigment forms after the inhalation of dust containing metallic iron. This pigment may be adsorbed by the coal particles in anthracotic lungs, and can then be detected only by incineration of fresh frozen sections. Coal particles will adsorb not only exogenous iron pigment but also endogenous hemosiderin, as in chronic congestion of the lungs.

C. ALEXANDER HELLWIG.

RELATIONSHIP BETWEEN TEMPERATURE AND OPTICAL PROPERTIES OF THE DOUBLY REFRACTIVE LIPOIDS IN THE ORGANISM. ZUISHUN IDA, Beitr. z. path. Anat. u. z. allg. Path. **88**:443, 1932.

Anisotropic fats were obtained from different organs of human cadavers, mammals, birds, amphibia, reptiles, fishes, insects and human parasites. It was determined at what temperature these substances lose their anisotropic properties or, on the other hand, regain them. Marked differences in this critical temperature were noticed in different species, in the different organs and in age. For instance, the lipoids of the testes and the suprarenals were anisotropic only at freezing temperature. The fatty substances of the intestines, cartilage, lymph nodes and brain showed anisotropism even at 100 C. (212 F.). In other organs the lipoids lost their anisotropic properties between room temperature and 100 C. These differences in optical properties between fats of different origin suggest that chemically the lipoids are not uniform substances.

C. ALEXANDER HELLWIG.

URIC ACID INFARCTS IN THE KIDNEY OF THE NEW-BORN. HANS HEINRICHS, Beitr. z. path. Anat. u. z. allg. Path. **89**:229, 1932.

Of 175 kidneys studied, 112 of which were from infants up to 3 weeks old and 63 from infants older than 3 weeks, 20 per cent had uric acid infarcts. The causes of death found in the positive cases were not in accord with the theory of Lubarsch that inflammatory processes predispose to the plugging of the renal tubules with crystals of uric acid. The highest percentage of infarcts was noticed in patients with nutritional disturbances (50 per cent). The opinion of Fahr, M. B. Schmidt and Aschoff that increased excretion and infarcts of uric acid in the new-born are caused by metabolic changes pertaining to respiration, nutrition and the regulation of heat during the first weeks of extra-uterine life is accepted. The enormous destruction of leukocytes during the first days of life may also play an important rôle.

C. ALEXANDER HELLWIG.

RELATION OF BILIARY SEDIMENT TO BILIARY CALCULI. R. SCHRADER, Beitr. z. path. Anat. u. z. allg. Path. **90**:304, 1932.

This article of sixty-seven pages is based on the microscopic study of the sediment of human bile obtained by postmortem puncture of the gallbladder and of dog's bile following a variety of experimental procedures. Five types of sediment or microliths are described. In the dog, simple stasis of bile in the gallbladder, such as follows ligation of a duct, leads to a marked concentration of bile

but not to the formation of microliths. Intermittent stagnation of bile, with the access of fresh bile, leads to the formation of green, waxy spherules and irregular masses (M1). These are composed of mucus and protein infiltrated by bile pigment. They were found also in human bile when there had been intermittent stagnation, of which process they are characteristic. In the dog, conglomeration of such material led to the formation of irregular pigmented concretions of considerable size; this was the only kind of concretion that could be produced experimentally in the dog. Similar concretions in the human gallbladder may be harder if they contain calcium. Infection and inflammation have no part in the formation of type 1 microliths. Pigment stones of the heavy earths may form in the biliary ducts as the result of stasis and toxic cholangeitis. Microliths of type 2 (M2) were seen frequently in human bile post mortem and less frequently in dog's bile. They are brown, doubly refractile, rod-shaped or in the form of coarse needles arranged radially, and consist of a calcium-protein-bilirubin complex. Microliths of the third type (M3) have the same composition and physical properties as M2, but are spherical. These two types of microliths occurred when there had been central venous engorgement of the liver, of which condition they are symptomatic. Microliths of the fourth type (M4) were the kind encountered most often in human bile. They consist of calcium and an amyloid-like material. They occur only in the form of true spheres, which are doubly refractile and may reveal a laminate or radiate arrangement. They are indicative of disturbed hepatic metabolism (parenchymatous hepatitis) and may be especially numerous in the various forms of cirrhosis. They may be white, green or yellow. The fifth type of microlith (M5) consists of greenish-brown, granular, irregularly rounded masses about the size of leukocytes. Their composition is unknown. They are found constantly in bile from the gallbladder in association with cholecystitis, hydrops or calculi. Except in the case of the greenish concretions that are formed by the agglomeration of type 1 microliths, these various kinds of sediment have nothing to do with the formation of stones and do not make up the centers of calculi, though they may be incorporated in stones. The center of pure cholesterol stones and of the common pigment-calcium-cholesterol calculi is formed by a protein meshwork which is the result of cholecystitis or cholangeitis.

O. T. SCHULTZ.

INORGANIC ASH SKELETON OF THE THYROID. G. MONSCH, Beitr. z. path. Anat. u. z. allg. Path. **90**:479, 1932.

The quantitative relationships and the morphology of the inorganic ash of the thyroid were studied in eighty thyroids by the incineration method of Schultz-Brauns. Within the follicles the ash of the colloid in the spodograms varied considerably in its morphology and often appeared as radiate or laminate masses. These variations are due to the pressure developed in the colloid during the incineration and are dependent on the original consistency of the colloid. They are influenced also by the time and the temperature of incineration. The variable ash content of contiguous colloid nodules, revealed by the ashed sections, was associated with the variable content of the nodules in the parenchyma. No correlation could be detected between the staining reactions of the colloid and its ash content, nor was there any correlation between age and ash content. The parenchyma of the thyroids contained more inorganic ash than did the colloid nodules.

O. T. SCHULTZ.

SPECTROPHOMETRIC ANALYSIS OF THE COLOR-PRODUCING SUBSTANCES OF THE SERUM. PIUS MÜLLER, Klin. Wchnschr. **11**:189, 1932.

Spectrophometric methods indicate the presence of three definite groups of chromophoric substances in normal and pathologic serums, hemoglobin absorbing at 414 millimicrons, lipochromes at 490, 460 and 425 millimicrons and bilirubin absorbing in a broad band with a maximal intensity of 450 millimicrons.

The absorption band for hemoglobin was found in all normal serums, but serums from patients with anemia, nephritis, diabetes mellitus and similar diseases

associated with a decrease in the hemoglobin content of the blood were more or less free from this band. The absorption bands for the lipochromes appear in the same positions in normal and pathologic serums, even in extracts made from the serums with purified petroleum benzine and carbon disulphide. Porphyrin, with an absorption band showing a maximal intensity at 406 millimicrons, was found in the serum of a patient with Biermer's anemia. The band disappeared when renal therapy was instituted. Müller believes that the intense yellow color in serum is not associated with bilirubin but is dependent on the hemoglobin content of the serum.

D. O. Rosbash.

Magnesium Content of the Blood. Erwin Becker, Klin. Wchnschr. **11**:202, 1932.

The magnesium content of normal serum ranges from 1.8 to 2.3 mg. per hundred cubic centimeters, with an average content of 2 mg. In nephritic disease without renal insufficiency the value is slightly increased, while in acute and moderate renal insufficiency the value increases to an average of 3.5 mg. The increase of the magnesium content in renal insufficiency does not parallel the degree of functional disturbance in all cases. Erythrocytes contain more magnesium than the serum, and the fluids contain more magnesium than calcium. Muscle contains large amounts of magnesium.

D. O. Rosbash.

A Digitonin Microdetermination of Cholesterol. P. O. Muhbach and C. Kauffmann, Klin. Wchnschr. **11**:284, 1932.

A nephelometric method which is considered to be as accurate as the gravimetric method is described for the determination of free and esterified cholesterol in 1 cm. of blood or serum. Serum, blood or tissue is extracted with Bloor's alcohol and ether mixture. The free and combined cholesterol are dissolved in acetone, and after a detailed process of purification the free cholesterol is dissolved in alcohol. The addition of digitonin and water produces a colloidal turbidity which is compared with a standard solution of pure cholesterol. A portion of the acetone solution is saponified with concentrated sodium hydroxide, and the esterified cholesterol represents the total cholesterol content of the free cholesterol. From 0.2 to 0.8 mg. of cholesterol can be determined. More concentrated solutions should be diluted.

D. O. Rosbash.

Nonprotein Carbon of the Blood in Circulatory Diseases. F. Kisch, Klin. Wchnschr. **11**:1500, 1932.

The nonprotein carbon of the blood is increased in cardiac diseases. The highest values were obtained in cardiac edema and passive hyperemia of the liver. In disorders with edema small amounts of carbon compounds are excreted in the urine, and in diseases without edema, large amounts. With improvement the residual carbon content of the blood decreases and the amount of carbon excreted in the urine increases. Relapse is indicated by an increase of the residual carbon content of the blood.

D. O. Rosbash.

Microbiology and Parasitology

The Accumulation of Iron in Tuberculous Areas. Valy Menkin, Am. J. M. Sc. **185**:40, 1933.

Repeated intravenous injections of ferric chloride are followed by an accumulation of iron in caseous areas of tubercles and by a definite increase in the time of survival of tuberculous rabbits. Studies of the changes in weight and comparison of the pathologic involvement in the lungs of the control and experimental animals

at various intervals indicate that the intravenous administration of ferric chloride protracts the course of the disease. Repeated intravenous injections of ferric chloride retard the development of tuberculous lesions. This is found by comparing the extent of the pulmonary lesions in control and experimental animals that have had the disease for the same length of time. AUTHOR'S SUMMARY.

THE NATURE OF THE NEGRI BODY. W. P. COVELL and W. B. C. DANKS, Am. J. Path. **8**:557, 1932.

The cytologic evidence presented, with that contributed by other authors, together with the experimental evidence, is not compatible with the protozoan or organismal theories concerning the nature of the Negri bodies. The contention that they arise from constituents of the nerve cell as a result of the action of the virus is in agreement with our observations, but we consider the evidence for the participation of the mitochondria, neurofibrils and nucleolus as inconclusive. Both the Negri bodies and the smaller atypical lyssa bodies are probably formed by alterations in the basophilic Nissl substance, the fundamental ground substance of the cell, and by addition of variable amounts of basophilic material of nuclear origin. There is no evidence that organisms on the borderline of microscopic visibility are cloaked with these cellular components in accordance with the chlamydozoal hypothesis. AUTHORS' SUMMARY.

A HISTOLOGICAL STUDY BY MICROINCINERATION OF THE INCLUSION BODY OF FOWLPOX. W. B. C. DANKS, Am. J. Path. **8**:711, 1932.

Following incineration at high temperature, the fowl pox inclusion body leaves a grayish-white residue consisting of minute particles of mineral ash. The location of this residue corresponds topographically to that part of the inclusion body which stains pink with erythrosin-azur. The minute particles of mineral ash correspond in relative size and location to the "Borrel bodies" and are the inorganic residue of these structures. There is evidence that the "Borrel bodies," having, as they do, a relatively large amount of inorganic material in them, might well serve as a locus for adsorption of virus. AUTHOR'S SUMMARY.

THE PATHOGENICITY OF THE BACILLUS OF CALMETTE-GUÉRIN. W. H. FELDMAN, Am. J. Path. **8**:755, 1932.

With a strain of B C G obtained from Calmette of the Pasteur Institute, a deliberate attempt was made to increase its pathogenicity by subculturing the organism on a glycerinated egg medium. Transfers were made every thirty days. From each succeeding subculture, four guinea-pigs were given injections — two intracerebrally, one subcutaneously and one intraperitoneally. The report deals with data obtained after the organism had been subcultured on glycerinated egg medium for fifteen generations. Of a total of fifty-eight guinea-pigs inoculated, lesions histologically indistinguishable from those of tuberculosis occurred in the tissues of eleven, and cultures of acid-fast bacilli were obtained from each. Although the majority of the lesions occurred in animals that had been given intracerebral injections, one animal that was given an intraperitoneal injection and another that was given a subcutaneous injection died with lesions of a tuberculous nature. So far, attempts have failed to promote a succession of tuberculous lesions by the reinoculation into guinea-pigs of infective material from lesions. The particular strain of B C G studied is not devoid of pathogenicity for guinea-pigs, and the assertion that the organism is innocuous cannot be accepted without reservations. Subculturing the organism on glycerinated egg medium at monthly intervals for a period of fifteen generations did not markedly enhance its virulence.

AUTHOR'S SUMMARY.

Immunology

SKIN REACTIONS TO HEATED POLIOMYELITIS VIRUS. A. B. SABIN, W. H. PARK and C. W. JUNGEBLUT, Arch. Int. Med. **51**:878, 1933.

There is at the present time no definite evidence for the existence of cutaneous allergy to the heat-inactivated virus of poliomyelitis in human beings, although such a possibility is not conclusively eliminated. Hence there is no basis for a skin test which would differentiate between susceptibility and resistance to the disease. Whether or not unheated virus may act differently in this respect is not known and must await the results of further investigations, which are naturally fraught with certain difficulties and remote dangers. FROM AUTHORS' SUMMARY.

ANTIGENIC RELATIONSHIP OF PROTEUS X19 TO TYPHUS RICKETTSIAE. M. RUIZ CASTANEDA and S. ZIA, J. Exper. Med. **58**:55, 1933.

There is a common antigenic factor in rickettsiae and Proteus X19 which explains the Weil-Felix reaction. AUTHORS' SUMMARY.

THE IMMUNOLOGIC SPECIFICITY OF BRAIN TISSUE. J. H. LEWIS, J. Immunol. **24**:193, 1933.

Suspensions of foreign brain tissue are strongly antigenic when injected into rabbits. A suspension of rabbit brain is not antigenic for the rabbit. Alcoholic extracts of all brains, including those of rabbit brain, are antigenic for the rabbit when activated with a foreign protein. Brain antiserums produced with a suspension of brain tissue and those produced with an activated alcoholic extract of brain are indistinguishable as to their content of antibodies that react with organs. Brain antiserums do not react with suspensions or alcoholic extracts of the liver, kidney, heart, spleen and lungs of homologous or all heterologous species tested. Neither do they react with blood serum, but they react strongly with both the suspension and the alcoholic extract of the brains of a group of animals representing mammals, birds and cold-blooded types. The brains of all animals tested are indistinguishable by complement-fixation reactions with an antibrain serum. Brain antiserums react strongly with either the suspension or the alcoholic extract of the testes of homologous and of all heterologous species tested. There is no qualitative difference between the reaction of a suspension and an alcoholic extract of brain, or between a suspension and an alcoholic extract of testes with an antibrain serum. The spinal cord and all anatomic parts of the brain react similarly with an antibrain serum. Lecithin (Merck's egg) does not react with an antibrain serum. Cholesterol (commercial) gives marked reactions.

AUTHOR'S SUMMARY.

CUTANEOUS EPITHELIUM IN IMMUNITY RESPONSE. L. DIENES, J. Immunol. **24**: 253, 1933.

In allergic (contact) dermatitis and certain cases of idiosyncrasy to drugs, the epithelium of the skin is probably sensitized. The hypersensitiveness of the epithelium develops by contact with the injurious agent in the same manner as the usual forms of hypersensitiveness. The tuberculin type of cutaneous reactions has many characteristics that suggest the direct participation of the cutaneous epithelium. The characteristic necrosis is often limited to the epithelium and a thin layer of connective tissue below it. The epithelium is involved early, before the macroscopic reaction is strong, and is often infiltrated with polymorphonuclear leukocytes, even in slight tuberculin reactions. The occurrence of necrosis has no direct connection with the size of the reaction or with the general sensitiveness.

AUTHOR'S SUMMARY.

COMPARATIVE PHAGOCYTIC ACTIVITY OF MACROPHAGES AND POLYMORPHONUCLEAR LEUKOCYTES. BALDUIN LUCKÉ ET AL., J. Immunol. **24**:455, 1933.

When macrophages and polymorphonuclear leukocytes are afforded an equal opportunity in vitro for contact with various kinds of particulate objects, they show, in the absence of serum, a similar degree of phagocytosis toward most kinds of particles tested. A notable exception is observed with small particles of collodion, which are more readily ingested by macrophages than by polymorphonuclears. The presence of or sensitization with immune serum, or of its globulin fractions, promotes phagocytosis by both kinds of cells to an approximately corresponding degree. The mechanism of bacteriotropin action is the same for both kinds of cells; that is to say, the interaction of the antigen particle and the immune serum causes a specific combination with and deposition on the antigen surface of antibody globulin, as a result of which both kinds of phagocytic cells are enabled to spread on and engulf the sensitized particle.

AUTHORS' SUMMARY.

PHAGOCYTOSIS OF TYPHOID BACILLUS. STUART MUDD ET AL., J. Immunol. **24**: 493, 1933.

Serums containing both flagellar and somatic antibodies against the typhoid bacillus and serums containing chiefly or only flagellar antibodies and chiefly or only somatic antibodies were prepared. These serums were tested in parallel agglutination and phagocytosis of flagellate typhoid bacilli to an equal degree by both macrophages and polymorphonuclear leukocytes. The bacteriotropin effect closely paralleled the agglutination. Sensitization to flagellar antibodies under the conditions of our experiments promoted phagocytosis of flagellate bacilli by both macrophages and polymorphonuclear leukocytes. The phagocytosis-promoting effect was inferior both in completeness and in titer to the agglutination; this difference is readily explained, however, by the secondary physical factors involved. The intracellular digestion of typhoid bacilli occurs with great rapidity in both types of phagocytes. The phagocytic behavior of the two types of cells was in essential agreement under the various conditions used in these experiments.

AUTHORS' SUMMARY.

ELECTRIC CHARGE OF ANTIBODIES. L. OLITZKI, J. Immunol. **24**:505, 1933.

Cataphoretic experiments with protein-making and protein-free agglutinins indicate that the results heretofore reported have been influenced by the protein present, and that the charge measured was that of the protein with which the agglutinin was associated. On the basis of the results with protein-free solutions, it seems that agglutinins (H and O type) carry a negative charge over a range of from p_H 10 to 3.4 and below that point are too sensitive to acid reactions to make measurement possible.

AUTHOR'S SUMMARY.

ANTIGENIC PROPERTIES OF RABIES VIRUS. L. C. HAVENS and C. R. MAYFIELD, J. Infect. Dis. **52**:364, 1933.

The results of agglutinin absorption with massive doses of antigen indicate that all strains of rabies virus contain the same antigenic constituents, but in varying quantities. Neutralization of heterologous strains of virus can be accomplished, provided sufficiently large amounts of serum are employed. The evidence obtained from a comparison of three strains of rabies virus before and after passage through the rabbit indicates that, associated with other changes which have been observed in fixed rabies virus, there is a pronounced rearrangement of antigenic structure. Whether these several differences, though occurring concomitantly, are independent or whether they are correlated it is impossible to state from the evidence.

AUTHORS' SUMMARY.

STREPTOCOCCAL ANTITOXIN AND ANTISTREPTOLYSIN. E. W. TODD, L. J. M. Laurent and N. GRAY HILL, J. Path. & Bact. **36**:201, 1933.

The antihemolytic and the antitoxic titers of serums from horses undergoing immunization with scarlet fever toxin frequently run parallel during the early stages of immunization. After prolonged immunization exceptionally high antitoxic titers may be attained without a corresponding increase of antistreptolysin. Serums from horses immunized with active streptolysin may contain large amounts of antistreptolysin, yet their antitoxic titers may remain relatively low. Patients with scarlet fever who give positive reactions to the Dick test on admission to the hospital may later give negative reactions without showing any change in the antistreptolysin titers of their serums. Rheumatic children whose reaction to the Dick test is positive may have abnormally high antistreptolysin titers. Antistreptolysin and streptococcal antitoxin are, therefore, distinct and separate antibodies.

AUTHORS' SUMMARY.

INFLUENCE OF HEAT ON DIPHTHERIA AND TETANUS FORMOL TOXOIDS. A. J. VAN DEN HOVEN VAN GENDEREN, J. Path. & Bact. **36**:319, 1933.

A number of comparative immunization experiments were made on guinea-pigs with heated and unheated diphtheria and tetanus formaldehyde solution toxoids. They led to the unexpected result that heating of tetanus toxoids from 60 to 70 C. improved their antigenic property considerably; heating to 80 C. had a rather deteriorating effect. With diphtheria toxoids, heating to 70 C. and higher had a deteriorating influence on the immunizing properties; heating to 56 C., however, resulted in improvement in a number of cases, but not in all. An explanation of this phenomenon cannot yet be given. Heating of diphtheria toxoid to 70 C. brought about a marked retardation of the flocculation reaction. In one case the flocculation did not appear at all. Even heating to 60 C. had a marked inhibitory influence.

AUTHOR'S SUMMARY.

IMMUNIZATION AGAINST YELLOW FEVER. A. W. SELLARDS and J. LAIGRET, Arch. Inst. Pasteur de Tunis **21**:229, 1932.

The results permit us to conclude that yellow fever virus, when weakened by numerous passages in the brain of mice, immunizes man against yellow fever. In the five subjects on whom observations were made, consecutive reactions to inoculation with the mouse virus were nil or insignificant. In a new series of seven trials, which will be the subject of a subsequent paper, three types of reactions occurred: febrile, delayed and atypical, which indicated the persistence in the mouse virus of a certain degree of activity for man, even after numerous passages.

FROM AUTHORS' CONCLUSION.

CROSS-IMMUNITY IN DIFFERENT FORMS OF TYPHUS. CHARLES NICOLLE and J. LAIGRET, Arch. Inst. Pasteur de Tunis **21**:251, 1932.

Tests of cross-immunity indicated that the typhus viruses studied—a historic strain (Tunis) and two animal strains (Mexico, Toulon)—are related. This is of practical importance, since they immunize against each other, but it does not prove identity. The preventive value of these viruses is not the same. The animal strains were more active against the historic strain than was this virus itself. Also they were more active against this virus than against themselves. In general, although they were of widely separated origin, the animal strains were more similar to each other than to the human virus. The results were the same, whether tested in the early stages, when the virus was still in the nerve centers (the period of premunition), or at a later period. This conclusion is also valid when the test is made with the virus employed for the first infection or with one of the other viruses. The results of tests of cross-immunity of typhus viruses are at variance with those of other tests in which the same method is used to differentiate them from other

exanthematic viruses. These tests differentiate the typhus viruses from the virus of Rocky Mountain spotted fever, as will be shown in subsequent articles, and from that of "button fever," as has been already shown by Burnet, Durand and Oliver.

AUTHORS' CONCLUSIONS.

Tumors

METASTATIC CARCINOMA OF THE HEART. C. H. MEAD, J. Thoracic Surg. **2**:87, 1932.

In cases of metastatic carcinoma of the heart, the lungs are invariably involved by primary or secondary carcinoma, hence the high frequency of pulmonary metastases generally may be a factor in increasing cardiac implants. Figures show, however, that in primary carcinoma of the lung there is less than 0.26 per cent cardiac metastasis. Direct extension is considered less likely than hematogenous metastasis by way of the pulmonary artery, the left atrium, the left ventricle and the coronary arteries. The author gives a complete case report with roentgenograms of the chest and a diagram of the massive primary bronchiogenic carcinoma of the right lung. The tumor extended through the right pulmonary vein to the left atrium, practically filling it, and continued through the mitral valve to end in a friable mass in the left ventricle. Mead also describes an invasion of the wall of the right atrium by carcinoma tissue, but it is not clear whether this was a direct extension or was metastatic. Associated findings were bronchopneumonia of the left lung and malignant infarct of the spleen. The cardiac involvement was not suspected clinically, and, as the author points out, few cases are diagnosed ante mortem.

J. STEWART.

PROPAGATION OF FUJINAMI'S FOWL MYXOSARCOMA IN DUCKLINGS. W. E. GYE, Brit. J. Exper. Path. **13**:458, 1932.

Fujinami's myxosarcoma of fowl has been propagated through eighteen generations in ducklings. The infective agent retains its power to infect chickens. In half-grown or in older ducks tumors form in response to injections of cell emulsions or of cell-free extracts, but the tumors retrogress.

AUTHOR'S SUMMARY.

PROPAGATION OF THE FUJINAMI FOWL-MYXOSARCOMA IN ADULT DUCKS. W. J. PURDY, Brit. J. Exper. Path. **13**:467, 1932.

Fujinami and Hatano found that a certain myxosarcoma of the fowl is propagable in ducks. Gye was able to confirm the observation in ducks of the Khaki Campbell variety, but only by using very young ducklings. It is now found that by the use of doses of tissue much larger than those given by Gye it is possible to propagate the Fujinami myxosarcoma in adult ducks of the Khaki Campbell variety through an indefinite number of generations. The greater efficacy of a large dose of minced tumor is not due to any greater energy of growth conferred on the cells of the resulting tumor. It is due to the fact that the resulting tumor starts in a greater number of primary foci, and reaches a correspondingly greater size before regressive changes have time to appear. AUTHOR'S SUMMARY.

PROPAGATION OF THE ROUS SARCOMA NO. 1 IN DUCKLINGS. W. J. PURDY, Brit. J. Exper. Path. **13**:473, 1932.

Rous sarcoma 1 has been propagated in ducklings for five tumor generations and presumably could be propagated in these birds indefinitely. Very young ducklings were used. They were of the Khaki Campbell variety. For the propagation of the tumor it was found necessary to use minced tumor tissue as the inoculum. The dose was 0.5 cc., given intramuscularly. Filtrates of duckling-grown Rous sarcomas do not produce tumors in ducklings — neither do filtrates of fowl-grown Rous sarcomas. Filtrates of duckling-grown Rous sarcomas do produce tumors

in fowls, and do so just as readily as filtrates of fowl-grown sarcomas. Thus Rous sarcoma 1 growing in ducklings is exactly like a mammalian tumor growing in a mammal: Within the species it is propagable by means of cell grafts, but not by means of filtrates. It is only because filtrates of duck-grown Rous sarcomas give rise to tumors in fowls, an alien species, that a filter-passing agent can be demonstrated. Minced tissue prepared from fowl-grown specimens of Begg's endothelioma gives rise to growing tumors in very young ducklings, but the tumors are never large and they soon disappear. Filtered extracts of the fowl-grown endotheliomas never produce tumors in ducklings. AUTHOR'S SUMMARY.

EFFECT OF TUMOUR REGRESSION AND TISSUE ABSORPTION ON THE SERUM. A. M. BEGG and H. A. A. AITKEN, Brit. J. Exper. Path. **13**:479, 1932.

Extensive bleeding or intratumoral injections of sodium oleate sometimes lead to regression of the Rous tumor in fowls. The presence of the Rous sarcoma does not increase the antitryptic property of fowl serum. The serum of fowls immune to cell inoculations of Rous sarcoma has high lipolytic power, and this statement applies also to the serum of animals which have received intramuscular or subcutaneous injections of surviving foreign tumor tissue. The presence of Rous, Mill Hill, "63," "37S," tar tumors or injected foreign tissue alters the serum of the tumor-bearing animals so that the point of flocculation with vanadate-acetic acid is displaced in the direction of lower p_H. AUTHORS' SUMMARY.

A FUNCTIONING ISLET TUMOR OF THE PANCREAS. W. G. BARNARD, J. Path. & Bact. **35**:929, 1932.

A woman, 40 years old, died from hypoglycemia and associated symptoms. At postmortem examination, a rounded tumor, 1.2 cm. in diameter, was found embedded in the head of the pancreas, projecting from its lower posterior border. The tumor was firm and grayish white. Microscopically, the general structure in the most characteristic parts of the tumor was strikingly similar to that of the islets. There were no metastases.

FAMILIAL AND BILATERAL TUMOURS OF THE CAROTID BODY. W. H. CHASE, J. Path. & Bact. **36**:1, 1933.

Two cases of "benign" neoplasms of the carotid body occurring in sisters have been described. In one instance the tumors were bilateral, appearing within an interval of six months. In the other the tumors and their histogenesis indicate that they are appropriately termed paraganglioma caroticum. The histologic study includes an investigation of the chromaffin-epinephrine relations and the demonstration of medullated and nonmedullated nerves. Factors possibly concerned in the occurrence of bilateral hyperplasia and neoplasia of the carotid body are indicated.

AUTHOR'S SUMMARY.

SIGNIFICANCE OF NERVE FIBRES IN HUMAN MALIGNANT NEOPLASMS. G. M. RYRIE, J. Path. & Bact. **36**:13, 1933.

A series of eleven cases of carcinoma was investigated to determine the presence or otherwise of nervous elements. The material used was obtained at operation. The technical difficulty of demonstrating with certainty axis cylinders was considerable. After extensive trial it was found that Gross-Bielschowski's silver impregnation method was the most satisfactory. When a portion of a nerve is destroyed by the advancing neoplasm, numerous new fibrils grow from the living axis cylinders of the proximal stump of the nerve trunk. These new axis cylinders not only grow within the perineural tube of the proximal portion, but penetrate into the neoplastic tissue. The process is exactly similar to what occurs after section of a peripheral nerve, and there seems no reason to suppose that the newformed axis cylinders exert any "trophic" influence on the neoplastic cells.

AUTHOR'S SUMMARY.

RETICULO-ENDOTHELIOMATOSIS, OVARIAN ENDOTHELIOMA AND MONOCYTIC (HISTIOCYTIC) LEUKAEMIA. R. GITTINS and J. C. HAWKSLEY, J. Path. & Bact. **36**:115, 1933.

A case of bilateral ovarian endothelioma in an infant aged 1 year is described. The growth resembled a reticulo-endotheliomatous process and was somewhat different from any ovarian endothelioma heretofore recorded. The neoplasms, though extirpated, were followed by general reticulo-endotheliosis with the blood picture of histiocytic leukemia and a high lymphocytosis of normal type. Endothelioma of the ovary is rare. Several varieties are recognized. Including the one here reported, only twenty histologically authenticated cases of monocytic (histiocytic) leukemia are on record. The observation of focal neoplasia (ovarian endotheliomas) and general (histiocytic) leukemia in the same patient within a few weeks is put forward as evidence of the essentially neoplastic nature of this type of leukemia.

AUTHORS' SUMMARY.

MESOBLASTIC TUMORS FOLLOWING INTRAPERITONEAL INJECTIONS OF 1:2:5:6-DIBENZANTHRACENE IN A FATTY MEDIUM. H. BURROWS, Proc. Roy. Soc., London, s. B, **111**:238, 1932.

Tumors were produced in rats by the injection of 1·2·5·6-dibenzanthracene into the right hypogastrium. The compound was given as an emulsion of an olive oil solution of the substance in water, the final concentration of the hydrocarbon being 0.1 per cent. Definite tumors were obtained in eight of ten rats within from twenty-three to forty-eight weeks. One rat probably had a precancerous condition when killed at twenty-six weeks, and the remaining one was not examined. The distribution of the tumors is given. The general type of cell was the spindle cell, but giant cells were frequently seen, with occasional pronounced polymorphism. These types were found coexisting in the same animal. No metastases were observed in extraperitoneal regions. The respective parts played by the hydrocarbon and the fat in the carcinogenesis are undetermined. L. E. SHINN.

PRODUCTION OF CANCER BY PURE HYDROCARBONS. J. W. COOK, I. HIEGER, E. L. KENNAWAY and W. V. MAYNEORD, Proc. Roy. Soc., London, s. B, **111**:455, 1932.

Tests for cancer-producing activity were made with several polycyclic, aromatic hydrocarbons. The only pure hydrocarbons which were found to produce carcinoma were 1·2·5·6-dibenzanthracene and some closely related compounds. The 1·2·5·6-dibenzanthracene shows undiminished carcinogenic power when highly purified. It has produced carcinoma when applied in a concentration of 0.003 per cent. Two hundred and thirty-three mice treated with this compound in benzene yielded seventy-seven epitheliomas and twenty-one papillomas. L. E. SHINN.

PRODUCTION OF CANCER BY PURE HYDROCARBONS. J. W. COOK, Proc. Roy. Soc., London, s. B, **111**:485, 1932.

Evidence is presented for the carcinogenic power of 6-isopropyl-1·2-benzanthracene. Several compounds containing the 1·2·5·6-dibenzanthracene system were found to produce tumors. The 5·6-cyclopenteno-1·2-benzanthracene was found to be highly carcinogenic. Rings attached to the 1·2 and 5·6 positions of the anthracene ring system may produce particularly effective compounds. L. E. SHINN.

INFLUENCE OF VITAL DYESTUFFS AND OF METALLIC COLLOIDS ON RESISTANCE TO TRANSPLANTABLE NEW GROWTHS. R. J. LUDFORD, Tenth Scientific Report of The Imperial Cancer Research Fund, 1932, p. 1.

Experiments have been described which show that resistance to the growth of transplantable tumors can be lowered by vital staining (*Speicherung*). The

types of resistance to which this applies are natural resistance, etc. Evidence is adduced for believing that the lowering of resistance is the result of interference with the function of cells derived from lymphocytes and monocytes, which segregate acid dyes. Such cells appear in large numbers around the site of inoculation during the development of immunity, and also around the margins of reabsorbing tumors, tumors that induce concomitant immunity and irradiated tumors. When any such tumors are grown in vitro there is an extensive outwandering of mononuclear cells. The results of these experiments indicate the possible danger of overdosage in the treatment of cancer with colloids and semicolloids, in cases in which the body may be offering some resistance to the malignant growth.

AUTHOR'S SUMMARY.

EFFECT OF VITAL STAINING ON THE DISTRIBUTION OF THE BROWN-PEARCE RABBIT TUMOUR. L. FOULDS, Tenth Scientific Report of The Imperial Cancer Research Fund, 1932, p. 21.

Intravenous inoculation of the Brown-Pearce rabbit tumor closely reproduces the main features of metastasis from tumors implanted in the leg or the testis. Whatever the method of inoculation, tumors are rarely found in the spleen, and they are relatively uncommon in the lungs and the liver. Vital staining with trypan blue greatly increases the incidence of tumors in the spleen, lungs and liver after intravenous inoculation. The bearing of the experiments on some problems of metastasis in man is discussed. It is suggested that some organs, notably the spleen, resist the establishment of secondary deposits by a local mechanism similar to that which opposes the "take" of grafts in laboratory animals. This defense is probably dependent on the cells of the reticulo-endothelial system.

AUTHOR'S SUMMARY.

CHANGES IN CARBOHYDRATE METABOLISM INDUCED BY RADIUM IRRADIATION OF TISSUES. H. G. CRABTREE, Tenth Scientific Report of The Imperial Cancer Research Fund, 1932, p. 33.

A study has been made of the effects of radium irradiation on the carbohydrate metabolism of surviving tumor and normal tissues. Also a limited number of observations have been made of metabolic changes induced by irradiating the Jensen rat sarcoma, rat testes and rat spleen in vivo. Studies in vivo are governed by the capacity of isolated tissues to survive in artificial mediums for relatively long periods. This is due to the latent period which must elapse before the criteria used in determining the effects produced by radiation become measurable. Tumors, testes and spleen were the only tissues of those examined which would satisfy this requirement. Irradiation in vivo with moderate doses gives results which are difficult to assess on account of the response of the whole animal. In the case of applications of large doses the accompanying impairment of function of vital organs introduces further complicating factors. The respiratory processes are always affected. In vitro, tissues under constant irradiation gradually lose their power of using oxygen after an initial period of some hours, during which no change is detectable. Control tissues meanwhile respire freely, though ultimately they suffer the same fate. Radium irradiation effects an acceleration of a naturally occurring degenerative process. Glycolytic processes are much more resistant to the damaging influence of radium irradiation. During the period of progressive decay of the respiratory power to a negligible value, glycolysis proceeds unimpaired. In vivo, similar effects are produced, though less rapidly. The delayed effect of radium irradiation on the Jensen rat sarcoma leads to a fall in magnitude of the respiration, or a damaging of its effectiveness in checking glycolysis, which results in the appearance of abnormally high aerobic glycolysis. On rat testis and spleen a fall in respiration is brought about without any corresponding rise of aerobic glycolysis. No differential action on the metabolism of tumor tissue, as against normal tissue, was observed as a result of radium irradiation. The conception that tumor tissue is inherently more vulnerable than normal tissue to irradiation is not supported.

AUTHOR'S SUMMARY.

EFFECTS OF RADIUM IRRADIATION ON THE SUCCINOXIDASE EXTRACTED FROM MUSCLE. H. G. CRABTREE, Tenth Scientific Report of The Imperial Cancer Research Fund, 1932, p. 71.

The effects of radium irradiation on a typical oxydase have been studied. Using comparatively large doses of radiation, an irreversible inactivation has been demonstrated. The degree of inactivation is a function of the time of irradiation, the thickness of the layer of enzyme extract and the intensity of the energy emission. Beta-radiation and gamma-radiation produce the same effect, differing only quantitatively. The possible rôle of such inactivation in the irradiation of tumors is discussed.

AUTHOR'S SUMMARY.

EXPERIMENTAL OBSERVATIONS ON THE EFFECT OF RADIUM ON A PRECANCEROUS SKIN AREA. W. CRAMER, Tenth Scientific Report of The Imperial Cancer Research Fund, 1932, p. 81.

The application of radium to a precancerous area of skin delays and even inhibits the development of malignancy. This effect was most marked when the precancerous conditions were not too far advanced and the dose of radium relatively large, as measured by the reaction of the skin. No evidence was obtained that radium, in the doses given, had an effect of breaking down the resistance of the skin to the development of malignancy. The application of radiotherapy in carefully graded doses to precancerous conditions in man is therefore strongly indicated as an effective measure for delaying and even preventing the development of malignancy. Further, when radiotherapy is applied to a fully developed malignant tumor in man, the possibility must be considered that a much larger part of the tissue or organ has been subjected to chronic irritation than that portion in which the malignant growth has developed, and that therefore even the apparently normal parts may be in a precancerous condition. For this reason the application of radiotherapy should extend over a much wider area than the malignant growth and its immediate neighborhood, in order to retard or prevent the subsequent development of a new malignant growth from the possibly precancerous cells. For instance, in the case of the breast, the treatment should extend over the whole organ.

AUTHOR'S SUMMARY.

EXPERIMENTAL OBSERVATIONS ON THE THERAPEUTIC ACTION OF RADIUM. W. CRAMER, Tenth Scientific Report of The Imperial Cancer Research Fund, 1932, p. 95.

The conceptions concerning the therapeutic action of radium fall into two main groups: the view which attributes it to a local and direct action on the irradiated area, and the view which attributes the therapeutic effect to a generalized indirect action operating either by itself or in conjunction with the local action. Experimental analysis of the action of radium shows that a general indirect effect plays no part in the regression of a malignant new growth. In the conception of a direct local action one can distinguish between the view that radium has a selective destructive effect on the malignant cells and the view that the regression of a tumor is brought about by an action on the stroma, or bed, of a neoplasm. The question at issue is of fundamental importance for the rationale of radiotherapy. At present this is based on the assumption that every malignant cell has to be destroyed by a direct local action in order to bring about the regression of a malignant neoplasm. This conception would necessitate the application of radium continuously over a long period, or at frequently repeated intervals, in order to subject the malignant cells to the direct lethal action of radium when they are most sensitive to it — that is to say, when they are preparing for mitosis. No conclusive evidence, clinical or experimental, in support of this view has been offered. Experiments on tissue culture are not conclusive, because they do not represent the conditions of a malignant neoplasm growing in a living organism, since the effects on the tumor bed and the reaction of repair are left out of con-

sideration. The experimental analysis presented in this paper shows that irradiation of a neoplasm damages both the tumor cells and the tumor bed, and that regression of the tumor is brought about by a combination of these two effects and the process of repair following on the damage to the tumor cells and their bed. This is accomplished by a dosage and under conditions which preclude the possibility that every malignant cell has received directly a lethal dose. If this view, rather than that of a selective destructive action on malignant cells, is taken as a basis for radiotherapy, it follows that radium should be applied so as to produce a uniform effect on the tumor as a whole, surrounding it from all sides, and that the dosage should be such as to produce a maximal injury limited to the tumor as a whole and consistent with an active reaction of repair and with the integrity of the normal epithelial tissues, which play no part in this reaction of repair.

AUTHOR'S SUMMARY.

Medicolegal Pathology

PNEUMONIA IN KEROSENE POISONING. J. I. WARING, Am. J. M. Sc. **185**:325, 1933.

Nine cases of kerosene poisoning with pulmonary complications are reported. Leukocytosis, with an increased percentage of polymorphonuclears, was a characteristic symptom. The cholesterol content of the blood appeared to be reduced, but no other chemical change was noted. Experiments on animals tend to confirm the clinical opinion that serious and fatal cases of kerosene poisoning are due to the aspiration of kerosene into the lungs, with the production of inflammation, edema and potentially fatal pneumonitis.

AUTHOR'S SUMMARY.

SILICIC ACID CONTENT OF SILICOTIC LUNGS. C. HACKMANN, Beitr. z. path. Anat. u. z. allg. Path. **90**:623, 1933.

The silicic acid content of the lungs was determined quantitatively by a gravimetric method, which the author considers more accurate than some of the colorimetric methods recently described. The silicic acid content is expressed in percentage of dried, pulverized lung. The lungs of two new-born infants and of an 18 year old girl contained only traces of silicic acid. The normal lungs of three adults, aged 38, 59 and 73, respectively, had a silicic acid content of 0.238, 0.089 and 0.184 per cent, respectively. The main portion of the contribution deals with the gross anatomic, histopathologic and chemical findings in the silicotic lungs of thirty-seven stone workers of the Ruhr district. In this group of lungs the iron content was also determined. The quantity of the latter bore no direct relationship to that of silicic acid present. The latter substance was increased in every instance. If the lungs were divided into three groups, namely, those with slight or moderate silicosis, those with well marked silicosis and those with extreme silicosis, it was found that the quantity of silicic acid bore a close relationship to the degree of pathologic change. The lungs of the second and third groups contained 1 per cent or more of silicic acid. Sixteen of the lungs were tuberculous. Tubercle bacilli were present in nine of twelve lungs of the first group, those with a relatively low silicon content and slight silicosis, and in six of thirteen lungs of the third group, those with extreme silicosis and high silicic acid content. They were present in only one of twelve lungs of the second group, which showed well marked silicosis and a silicic acid content of from 2.5 to 3.5 per cent. In the case of two of the inhabitants of the Ruhr district, it was known that they had not been engaged in an occupation that subjected them to the inhalation of stone dust for fifteen and ten years, respectively, before death, although they had originally been stone workers. The lungs presented well marked silicosis and contained 3.05 and 2.49 per cent, respectively, of silicic acid. These findings are interpreted as indicating that silicon, when it has been deposited in the lungs, is not readily removed and continues its harmful action. Although the quantity of dust inhaled may be influenced by the type of breathing and by other mechanical factors, the degree of silicosis

appears to depend directly on the quantity of finely divided silicious material that reaches the air spaces of the lung. The pathologic and chemical findings in four cases of silicosis that came to necropsy at Göttingen are also presented. These persons had worked with various kinds of stone, but all unlike that of the Ruhr district. In this group, the silicic acid content of the lungs was increased, but the degree of silicosis could not be correlated with the quantity of silicon present, as in the Ruhr group. The findings in a group working with one kind of stone are not therefore exactly comparable with those of another group working with a different kind of stone. In three cases in which the amount of silicon in the liver and spleen was determined, the quantity was appreciably increased. In two of these cases, in which the kidney was also examined, this organ contained only traces of silicic acid.

O. T. SCHULTZ.

GROUP IDENTIFICATION OF STAINS OF HUMAN MATERIAL. L. CHRISTENSEN, Deutsche Ztschr. f. d. ges. gerichtl. Med. **20**:89, 1932.

Human semen, urine, saliva, amniotic fluid, tears, exudate and tissue contain the same receptors as the homologous blood corpuscles, by means of which the blood group of a person may be determined by appropriate tests. Only a small amount of material is required for such tests. In medicolegal work it may be of importance to identify the group of the blood or other material in stains of human origin.

HEMORRHAGES IN THE CERVICAL LYMPH NODES IN DEATH BY HANGING. L. JANKOVICH and J. INCZE, Deutsche Ztschr. f. d. ges. gerichtl. Med. **20**:122, 1932.

Above and below the mark made by the constricting cord one finds, in all the lymph glands of the neck, not only signs of congestion and stasis, but also hemorrhages, as a direct effect of the compressing force. These microscopic observations are never absent if the person was hanged while alive. Occasionally extravasations may be found in bodies which have been hanged after death, but such extravasations have no destructive character. Experiments made on animals disclosed that hemorrhagic infiltration of the cervical lymph nodes develops in a manner identical with that observed in human beings.

E. L. MILOSLAVICH.

EXPERIMENTAL DEATH BY DROWNING. M. HIRAI, Deutsche Ztschr. f. d. ges. gerichtl. Med. **20**:134, 1932.

From observations on submerged rats, the author divides the process of death into three phases: that of initial struggle followed by that of defenselessness and ending with the stage of apparent asphyctic death. At the beginning of the second stage the fluid enters the lungs and the respiratory function ceases. Even in the third stage attempts at resuscitation were successful, but only if the obstructing fluid was removed from the upper respiratory tract.

E. L. MILOSLAVICH.

PUPILLARY REACTIONS AFTER DEATH. K. RITTER, Deutsche Ztschr. f. d. ges. gerichtl. Med. **20**:144, 1932.

Dilated pupils, as usually observed immediately after death, begin to contract equally not earlier than from seven to eight hours after death. This contraction is slow and gradual, until a width of from 2 to 3 mm. is reached during the next ten to fifteen hours. The pupils may then remain in this condition up to twenty hours after death. A slight dilatation and, later on, deformation follow. On the instillation of atropine, physostigmine (eserine), cocaine and epinephrine hydrochloride after death, the pupils exhibit the same reactions as they would have exhibited during life. With atropine, dilatation was obtained twenty hours after death, even after cadaveric rigidity of the muscles of the iris had set in.

E. L. MILOSLAVICH.

LETHAL POISONING WITH CHENOPODIUM OIL. A. IBRUS-MAEAER, Deutsche Ztschr. f. d. ges. gerichtl. Med. **20**:158, 1932.

At the autopsy of a 3 year old boy whose death was attributed to poisoning with chenopodium oil, marked cerebral edema was striking, the brain weighing 1,500 Gm. Chenopodium oil, while abolishing the otolithic reflexes, stimulates the reactions of the semicircular canals, which explains the clinical aural symptoms, such as ringing in the ears, dizziness and partial deafness, the latter often persisting in nonfatal cases.

E. L. MILOSLAVICH.

ACTIVITY OF PERSONS WITH GUNSHOT WOUNDS OF THE HEAD. G. ROOKS, Deutsche Ztschr. f. d. ges. gerichtl. Med. **20**:201, 1933.

In suicidal attempt, a man, aged 30, shot himself in the right temporal region; the outlet of the bullet was found in the center of the left side of the forehead. Two and a half days later, during which interval he was able to be up and around, the first symptoms of meningitis appeared, and death ensued three days afterward. Autopsy disclosed splintering of the frontal bones and destruction of the frontal lobes of the brain. In instances in which vital centers or motor areas in the brain have not been destroyed, the injured person is still capable of activity, provided that cerebral concussion does not render him unconscious.

E. L. MILOSLAVICH.

NATURE OF THE TRANSVERSE MARK IN THE NAILS IN ARSENICAL POLYNEURITIS. R. WIGAND, Deutsche Ztschr. f. d. ges. gerichtl. Med. **20**:207, 1933.

In nonlethal cases of arsenic poisoning, about two months after the ingestion of the poison, all the finger-nails show a transverse, white-gray band, about 1 mm. in width (Mees mark), which finding is of great diagnostic value. The band is somewhat similar to that observed in thallium poisoning, and contains ten times as much arsenic as the apparently normal parts of the same nail. The Mees mark represents a deposit of arsenic owing to impregnation of the nail substance.

E. L. MILOSLAVICH.

THALLIUM POISONING. G. BERG and R. BERG, Deutsche Ztschr. f. d. ges. gerichtl. Med. **20**:215, 1933.

Only three instances of murder by thallium poisoning are recorded in the literature. The clinical picture, as well as the observations at autopsy, are comparatively indefinite and negative. Swelling, congestion and hemorrhages of the mucous lining of the gastro-intestinal tract are usually present. Ordinary or routine chemical analysis of the organs fails to detect the presence of thallium. A special chemical examination is required. This is described in detail. The spectroscopic method, however, is a more sensitive, simpler and quicker means of detection.

E. L. MILOSLAVICH.

CHANGES IN THE SKIN CAUSED BY ELECTRIC CURRENT. G. STRASSMAN, Deutsche Ztschr. f. d. ges. gerichtl. Med. **20**:239, 1933.

In lethal electrocution the gross and microscopic changes of the skin at the site of the electric lesion are identical with those which can be produced by electric current when applied to a dead body, when even deposits of copper may be found in the altered tissues. The intensity of the electric injury depends on whether the skin is moist or dry at the time of the contact; in the latter instance, the changes are more severe. The occurrence of a spark and steam, with the development of a crater-like defect, are regularly observed at the site of the positive pole, if the skin is dry. However, if the skin is moist, vesicles appear, which rapidly burst and then dry, and a yellowish, only slight depression of the skin is formed. At the site of the negative pole, sparks and the effects of burning never occur, and the micro-

scopic alterations are of lesser extent. A 40 year old person who came in contact with a 10,000 volt current sustained an extensive deep burn of the entire arm and died fourteen hours later. Autopsy disclosed diffused fat embolism of the lungs and moderate fat embolism of the kidneys and spleen, which finding must be considered in the cause of death.

E. L. MILOSLAVICH.

INFANTICIDE BY BURNING. WERNER RADTKE, Deutsche Ztschr. f. d. ges. gerichtl. Med. **20**:267, 1933.

The ordinary tests for proof of live birth cannot be applied in cases of burning. Uninflated lungs with charred areas will float, and the stomach and intestines are rendered friable. If microscopic examination of burned parts of lungs discloses the presence of foreign material, this finding not only may be of importance in determining whether the infant was born alive, but may also lead to correct conclusions as to the cause and manner of death. The presence of soot in the respiratory tract must be carefully evaluated, since it does not conclusively prove that the infant was alive when burned. Sudan staining of the microscopic sections of the lung may be helpful in instances of aspiration of amniotic fluid. Since carbon monoxide cannot always be demonstrated in the blood taken from the cavities of the heart, microscopic analysis of the pulmonary tissue, even of the smallest charred remnants, should not be omitted, as it is the only remaining test which may yield important information.

E. L. MILOSLAVICH.

Technical

MICROTECHNICAL DEMONSTRATION OF INSOLUBLE LIME SALTS IN TISSUES. G. GÖMÖRI, Am. J. Path. **9**:253, 1933.

Cut or saw thin blocks of fresh tissue from 1 to 2 mm. thick. Fix in an 80 to 96 per cent solution of alcohol, or boil in one of the solutions mentioned. After this, wash the blocks in distilled water for from three to four hours. Impregnate in a 1.5 per cent solution of silver nitrate for from six to ten days. Change the silver solution once or twice. Wash for from three to four days in distilled water changed daily four or five times, until the last washing water, when decanted, does not show the slightest turbidity when mixed with hydrochloric acid. Reduce in a 5 per cent solution of sodium hypophosphite. Before use add 4 or 5 drops of tenth-normal solution of sodium hydroxide to each 100 cc. of the reducer. Keep the blocks in the reducer for from four to eight days. Wash in running water for from three to four hours. Fix in a 3 to 5 per cent solution of sodium thiosulphate for two days; then wash in running water for at least twenty-four hours. Decalcify in a 6 to 8 per cent solution of sulphosalicylic acid. Wash, embed, and so on.

In sections prepared in this way lime salts stand out in deep black with striking clearness on an unstained background. The preparations are said to be durable.

PREGNANCY TEST: PREMATURE ESTABLISHMENT OF VAGINAL ORIFICE IN IMMATURE ALBINO RATS BY INTRAPERITONEAL INJECTIONS OF URINE. G. L. KELLY, J. A. M. A. **100**:1010, 1933.

Intraperitoneal injections of from 5 to 15 cc. of urine from pregnant women will cause premature establishment of the vaginal orifice in the albino rat weighing from 30 to 40 Gm., usually within from seventy-two to eighty-four hours. Intraperitoneal injections of the same amount of urine from nonpregnant women will not cause such premature opening of the vagina. Two animals should be used, and the opening of the vaginas of both is read as positive; if the result is doubtful in one, the test should be repeated; if no result is obtained in either within ninety-six hours, the test is considered negative. If the vagina is open and the orifice obscure, one may see it by holding the animal by the neck and shoulder and pulling strongly on the base of the tail. In this maneuver the abdomen should not be compressed. The main advantages of the test are simplicity and ease of reading the result.

AUTHOR'S SUMMARY.

Society Transactions

NEW YORK PATHOLOGICAL SOCIETY

Regular Meeting, March 23, 1933

PAUL KLEMPERER, *President, in the Chair*

THE THYMUS IN INFECTIOUS DISEASE. MELVIN C. KIMBALL.

It has been the impression in certain of the hospitals for patients with communicable diseases that there was an unduly high incidence of infections in persons who presented definite lymphoid hyperplasia at autopsy, which suggested the possibility of a constitutional factor as a contributory cause of death. This feeling was considerably strengthened during the epidemic of poliomyelitis in 1931, and it was resolved to test the truth of this impression by tabulating the weights of the thymus and spleen as representative organs. The weight of the spleen was much too erratic to serve as a reliable index. The weight of the thymus was adopted as more constant.

This report is based on the weights of 345 thymuses removed at autopsy in cases of infection. The weights are grouped according to the ages of the patients and tabulated against the duration of the illness in each instance, for each of the five major communicable diseases, poliomyelitis, diphtheria, scarlatina, measles and pertussis, as compared with the average figures for the entire series. Any such procedure is open to the criticism of the absence of agreement as to a table of normal weights. The average figures used for comparison in this study lie about midway between the low estimates of Bovaird and Nicoll and the high figures recorded by Boyd in her exhaustive studies.

In 80 cases of poliomyelitis, the average weight of the thymus paralleled and was constantly above the general average. In diphtheria, it again paralleled the general average, but dropped a little below it. In scarlet fever, the cases were too few in number to give a reliable index, and the weight seemed rather erratic, but tended to approach that in diphtheria. In measles, there seemed to be a low average figure in spite of the relatively short course of the disease. In pertussis, there was a definite diminution in the weight of the thymus, dependent in part on the nutritional stage of the child during the prolonged course of the disease. The particular point of interest in this study was the confirmation of the impression that the constitutional factor seemed to play a fairly definite part in poliomyelitis.

DISCUSSION

PAUL KLEMPERER: What is the histologic picture of the lymphatic tissue in poliomyelitis, not so much in the thymus, but in the spleen and lymph nodes? What is the condition of the so-called secondary follicles in this disease?

LAWRENCE W. SMITH: The follicles are almost regularly definitely enlarged, with large germinal centers, many of them showing beginning necrotic changes. This is true not only of the follicles in the spleen, but of the lymphoid follicles in the mesenteric and other lymph nodes and in Peyer's patches in the intestine.

PAUL KLEMPERER: Is the condition similar to diphtheria?

LAWRENCE W. SMITH: Yes, in the milder form.

AN UNUSUAL CASE OF FAULTY BLOOD GROUPING DUE TO AUTO-AGGLUTINATION. PERRY J. MANHEIMS and E. K. BRUNNER.

A patient was admitted to the hospital with a hemoglobin reading of 15 per cent, a red cell count of 780,000 and a blood picture of myelogenous leukemia.

A routine blood grouping seemed to show an A B (Jansky 4) group. Nevertheless, cross-matching with the blood of an A B donor showed agglutination of the donor's red cells by the patient's serum, and vice versa.

When the patient's blood was tested, marked auto-agglutination was present. A regrouping was done after washing the red cells with physiologic solution of sodium chloride, and this time there was no agglutination with standard serum of group 2 or 3. The blood was reclassified as of group O (Jansky 1), and cross-matching with the blood of an O donor, the patient's washed red cells being used, showed compatibility. A transfusion was given without reaction.

The assumption was that because of the extreme anemia of the patient the citrated suspension of red cells used in the original grouping contained a large amount of serum and the agglutination was due to the auto-agglutinins contained in this serum, or that the agglutination was due to the auto-agglutinins which the red cells of the patient had absorbed from her serum when kept at a temperature lower than that of the body.

DISCUSSION

MAX LEDERER: I think that this difficulty could have been avoided easily by taking a small amount of the patient's whole blood in citrate; if there is agglutination with both A and B serum, examination of the whole blood will reveal whether there is any auto-agglutination. Our laboratory makes it a rule whenever A B agglutination is observed to examine the patient's whole blood in citrate in order to avoid a mistaken conclusion that the blood is of group A B.

ARTHUR SCHIFRIN: In 1927, a specimen of blood from a patient whose condition was later diagnosed as hemolytic jaundice was submitted to the laboratory of Dr. Shwartzman at Mount Sinai Hospital. The blood was typed as of group 4. A donor of group 4 was called, and a cross-agglutination test was made, which showed the two specimens of blood to be incompatible. It was found that there was auto-agglutination. Since that time, in all cases of blood dyscrasia of any type, the custom has been to put a drop of saline solution on a slide whenever a determination has been made of group 4. Dr. Rosenthal pointed out at that time that in cases of blood dyscrasia this is necessary.

RALPH G. STILLMAN: These instances of auto-agglutination are much more frequent than one would expect from an inspection of the literature. One has constantly to bear in mind the possibility of auto-agglutination when making a test for transfusion, and when necessary one should check the results either by examining the patient's own blood in saline solution or by making a grouping by examination of the patient's serum with cells of known groups. My associates and I have found that the use of citrate is not altogether satisfactory, because it tends in many instances to slow up the reaction of the cells with the type serum used for grouping, and unless this is carefully watched, it is likely to introduce an error.

MENDEL JACOBI: Several instances of auto-agglutination have recently been encountered at the Beth Israel Hospital. One was in a case of acquired hemolytic jaundice, a second in a case of myelogenous leukemia, and a third in a fatal case of staphylococcic septicemia. In studying the question in some detail—and it is now made a routine practice at this hospital to look for auto-agglutination in all specimens of blood typed, at room, incubator and icebox temperature—a rather high incidence of this phenomenon was found distributed through all the blood groups. Recently I came across a family in which though none of the members showed any pathologic condition, auto-agglutination was prevalent, apparently distributed according to mendelian principles.

THE SO-CALLED BRENNER TUMOR OF THE OVARY (FIBRO-EPITHELIOMA MUCINOSUM BENIGNUM). ALFRED PLAUT.

In the last few years I have observed 8 cases of the so-called Brenner tumor (a detailed description is given in the *Archiv für Gynäkologie* **153**:97, 1933). The

growths were diagnosed as benign fibro-epithelial tumors with clear cells. All were small and firm. They were found accidentally, some of them at operation and 2 at autopsy. They did not give clinical symptoms. The uterine bleeding which was present in some patients could be explained by other causes.

One of the tumors, as shown in the slides, forms a small protrusion on the surface of a gyrate ovary. Under magnification with a hand lens a large calcific area can be seen and the largest of the epithelial masses are recognizable. A characteristic low power field shows the numerous, partly solid, partly hollow epithelial masses spreading as an irregular network through dense stroma which is similar to ovarian stroma. Some of the epithelial masses are surrounded by a thin (occasionally thick) hyaline coat. A few of the epithelial structures are entirely hollowed out. Generally, long sections show more solid portions, thus demonstrating that the hollowing-out is restricted to a part of the epithelial structure. At higher magnification the cells appear uniformly large and clear, with distinct outlines, similar to those in the upper layers of the epidermis. There are, however, no epithelial fibrils. The cells near the central cavity, which is filled with mucin, may be exactly like the other cells or they may arrange themselves like a lining epithelium. The formation of mucin sometimes takes place simultaneously at many spots. While in most of the epithelial structures the outer layers look like the others, there are some with a distinct basal layer characterized by smaller cells and deeper-staining nuclei. The formation of mucin and hollowing-out may result in destruction of the epithelium, leaving cavities seemingly in the stroma proper. In some specimens the hollowing-out leads to the formation of mucinous cysts, which are lined with a single layer of high cylindric, mucin-secreting cells such as are customarily seen in a pseudomucinous cystoma. Not only are there all gradations, from solid epithelial masses to glandular structures similar to and in some instances directly related to pseudomucinous cystoma, but on serial section the continuity between a characteristic Brenner tumor and ordinary pseudomucinous cystoma is evident. In the narrow glandular ducts in the wall of a pseudomucinous cystoma, the beginning hyalinization of the surrounding stroma indicates the spot where the neighboring sections will show continuity with a Brenner tumor.

The epithelium is the most important and active part of the tumor. One solid epithelial structure protruding from the main tumor into ordinary ovarian stroma is surrounded by stroma cells which are arranged parallel to each other and to the outline of the epithelial structure, forming a striking contrast to the irregularly interwoven ovarian stroma. There are other evidences that the tumor influences the surrounding tissue. The peritoneal epithelium has a tendency to grow around small tumors, and one of them seems completely isolated from the rest of the tissue by a peritoneal cleft.

A miniature Brenner tumor was found in the torn wall of a lutein cyst in the ovary of a young woman. As may be seen in the sections, only a short distance from this spot other very small characteristic Brenner tumors are located. In the same piece of tissue there are Walthard cell rests, solid as well as hollow. At points it is impossible to say whether the mass is a Walthard rest or a small portion of a Brenner tumor. In the same specimen continuity between epithelial masses of the Brenner tumor and the lining peritoneal epithelium can be observed in serial sections.

The Brenner tumor, like the ovarian fibroma, contains very few blood vessels. In the elastic tissue stain one sometimes sees a tumor between the remnants of elastic lamellae and blood vessels. This cannot be interpreted as a malignant growth. The blood vessels have been destroyed mechanically by pressure and kinking, and the tumor grows between the dead remnants of the vascular walls. The large amount of epithelial tissue in the Brenner tumor has led to its being considered malignant. None of the patients whom I have observed has shown evidence of recurrence or metastasis. The cases, however, are recent (none having been observed for more than four years). When a Brenner tumor is found together with metastatic carcinoma, the diagnosis may become difficult.

The name proposed, "fibro-epithelioma mucinosum benignum," is intended first to designate the unusual feature that mucin is formed within a nonglandular epithelial tissue. This, however, takes place in normal tissues as well, for instance in the prostate of the new-born and occasionally in the prostate of the adult. I consider the benignancy of the tumor to be sufficiently established to permit the inclusion of the term "benignum" in the name. I should like to include in the name a reference to the compact character of most of the tumors, but the presence of many cysts does not permit this.

The number of cases described is not large enough for statistical evaluation. In most features these cases resemble the cases reports of which were collected by Robert Meyer. It is not yet known how frequent, or how rare, the tumor is. Brenner, in 1907, observed 3 cases within one year in Frankfurt; Meyer saw only 4 in the course of twenty years. It is astonishing that I have seen 8 in New York within five years. Statistics on the frequency of the tumor should be based on autopsy material as well as on gynecological material. The fact that in my gynecological material the tumors were found combined with other ovarian tumors does not prove anything, since these operations were undertaken for the symptoms caused by the other tumors. I have had the ovaries in 75 cases carefully sectioned without finding a Brenner tumor. In cases in which a Brenner tumor has been present in one ovary, nothing definite has been learned about the condition of the other ovary. In 1 instance only (that of Schiffmann) was a Brenner tumor found in both ovaries, and it was of microscopic dimensions. A complete serial examination of the other ovary was made in 1 of my cases, but no Brenner tumor was found, nor even Walthard rests. The Brenner tumor can develop in ovaries containing many Walthard rests and in ovaries containing none. One may consider the development of a Brenner tumor from a Walthard rest as tumorous growth without differentiation, while certain pseudomucinous cystomas represent tumorous growth with specific differentiation. I do not believe that all the so-called Walthard rests have existed from the embryonic period; I am convinced that they can originate during life from the peritoneal epithelium. On this point I am in full accord with Robert Meyer.

The youngest patient in my series was 20 years old, and the oldest, 73. No Brenner tumors have been reported in children. But the Walthard rest which Akagi found in the ovary of a 9 year old girl may be called the epithelial part of a very small Brenner tumor.

DISCUSSION

PAUL KLEMPERER: It is obvious that there is no discussion from the floor because of the rarity of these tumors. At Mount Sinai Hospital only 2 tumors of this type have been seen in the last twenty years. I think that in Dr. Frank's book (Gynecological and Obstetrical Pathology, New York, D. Appleton and Company, 1922) there is a picture of a tumor called a folliculoma which belongs to this type, and this shows that the growth has not been recognized until lately. Dr. Plaut deserves the credit for having called attention to these tumors.

In regard to the formation of mucin in other locations, I should like to mention, since Dr. Plaut spoke of such instances in the prostate, Brunn's epithelial nests in the bladder. One finds them frequently, and it is interesting that from these cell nests with formation of mucin malignant tumors may originate. I recently saw one in a normally formed bladder; it is in the exstrophic bladder that one most often finds the mucous cell nests which lead to carcinoma.

ALFRED PLAUT: The case at Mount Sinai Hospital that Dr. Klemperer alluded to is that of Geist, I believe. He closed his paper in 1922 with the remark that he did not want to give the tumor a name; and he described it merely as originating from an embryonal rest. The further development has substantiated that.

As to cell nests in the bladder, true gelatinous carcinomas may arise from such nests even as high as in the renal pelvis. I saw a gelatinous carcinoma in the pelvis of a kidney which could not be explained in any other way.

I may repeat that I had had the ovaries in 75 cases sectioned in very thin slices in the hope of finding a Brenner tumor and have not found any.

MALIGNANT NEPHROSCLEROSIS AND PERIARTERITIS NODOSA. SADAO OTANI.

Two cases are presented of malignant nephrosclerosis associated with periarteritis nodosa in other organs. Within the kidneys but one vessel was found which showed the typical fibrinoid necrosis of the media. As vascular alterations these organs presented chiefly the excessive intimal proliferation of the interlobular arteries and the necrosis of the arteriolar walls that have been described in malignant nephrosclerosis. The association with periarteritis nodosa raised the question whether these observations did not conclusively prove the inflammatory nature of the vascular alterations in malignant nephrosclerosis, a contention championed by Fahr. However, the prolonged duration of the disease and the finding at autopsy of peracute periarteritic lesions associated with advanced sclerotic lesions of the renal vessels suggested that the association might just as well be a coincidence.

DISCUSSION

ALFRED PLAUT: Arteriolitis comes into its own rather slowly. When one pays special attention to the arterioles, one finds arteriolitis more frequently than one would expect from the current literature. Some of the members of the society may remember the paper presented about a year ago by Drs. Helpern and Trubek (Isolated Necrotizing Arteritis and Subacute Glomerulonephritis in a Case of Gonococcal Endocarditis, ARCH. PATH. **14**:266, 1932). The gallbladder is a favorite site for periarteritis nodosa. Only a short time ago a patient was operated on in Beth Israel Hospital for acute cholecystitis, and the slides gave a picture of periarteritis nodosa. It is not yet known what other organs of this patient may contain the same lesion. Lesions which might be called periarteritis nodosa have been found in the testicles, the gallbladder and the eyes of patients with general infections—for instance, recently in a child with a general streptococcic infection probably starting from streptococcic pneumonia. How far these lesions conform with what is called periarteritis nodosa is another question. The present interest centers about the arteriolitic lesions found in people who do not suffer from infectious disease. I have seen arteriolitis in about 30 appendixes in the last few years. These were not inflamed appendixes, but those removed in the course of gynecological operations and other appendixes without inflammatory lesions. The common link seems to be an immunologic condition, some susceptibility of portions of arteries or arterioles which leads to necrosis. Whether or not the degenerative change in the wall of the vessel is followed by an inflammatory reaction depends on unknown conditions. I have expressed the feeling before that probably the pathology of the arterioles will occupy more space in textbooks of pathology a few years from now. Dr. Moon in Philadelphia told me that similar lesions occur in rabbits with experimental streptococcic infections. I accidentally saw an arteriolitic lesion in the skin of a mouse.

PURULENT THROMBOPHLEBITIS OF THE PULMONARY VEIN. WILLIAM ANTOPOL and COLEMAN B. RABIN.

Cases of infective thrombophlebitis of the pulmonary veins may be divided into two groups, the first consisting of those in which the small branches are involved, and the second in which there is infection of the larger radicles. Cases of the first type are often discovered only by the aid of the microscope. In these cases the thrombophlebitis may give rise to sporadic metastatic lesions in various parts of the body. In those of the second type a general infection ensues and gives rise to the picture of sepsis. Since the pulmonary veins enter the left side of the heart, emboli and infected infarcts are common.

The material on which this report is based consisted of 14 cases in which the larger pulmonary veins were involved. In 11 of these cases the initial focus

of infection was situated within the lung. The pulmonary disease was of a destructive type, either suppurative or gangrenous.

In 4 of the cases the primary lesion was suppurative bronchopneumonia. In 2 of these Streptococcus haemolyticus was the causative organism; in 1, Pneumococcus type III, and in 1, either an anhemolytic streptococcus or a pneumococcus of type IV. In 7 cases the primary lesion was a gangrenous abscess of the lung, and the invading organisms consisted of a mixture of anaerobic bacteria. In 2 of these cases the general invasion was probably the result of laceration or incision of a vein at operation. The healing of the lesions is demonstrated by the finding of a smooth-walled arteriovenous aneurysm two years after spontaneous healing of a gangrenous pulmonary abscess.

Thrombophlebitis of a pulmonary vein may occur in association with metastatic lesions of the lung secondary to a primary focus of infection somewhere else in the body, and it may serve to cause a general infection or sepsis even if the original infection is inadequate to do so. Three of our cases fall into this group. The importance of these lesions in maintaining a general infection again depends on the size of the vein invaded.

PYLEPHLEBITIS COMPLICATING GANGRENOUS PULMONARY ABSCESS. C. B. RABIN and SYLVAN MOOLTEN.

Suppurative pylephlebitis is usually secondary to a suppurative lesion within the gastro-intestinal tract. Its association with putrid pulmonary abscess is exceedingly rare according to the literature; nevertheless, we have observed 5 cases. The transport from the focus of suppuration within the lung is always through an infection of a pulmonary vein in the region of the abscess which enters the general circulation by way of the left side of the heart. Infection of small veins gives rise to single metastatic foci, and infection of larger veins, to multiple foci throughout the body.

The mechanism underlying suppurative pylephlebitis complicating pulmonary abscess is found to be a metastatic or an embolic abscess within the spleen. Infection of a branch of the splenic vein is demonstrable at the site of this abscess and produces involvement of the trunk of the splenic vein, with subsequent spread into the portal vein and its intrahepatic radicles. The pylephlebitic abscesses may secondarily involve the hepatic veins from which the bacteria enter the greater venous circulation. Metastatic pulmonary abscesses may occur in this manner.

Jaundice was present in 3 of our 5 cases of pylephlebitis complicating pulmonary abscess; it was not observed in any other case of pulmonary abscess in a series comprising well over 250 cases. It may be considered pathognomonic of this complication. Marked swelling and tenderness of the liver support the diagnosis. (Direct transdiaphragmatic spread of a pulmonary abscess into the liver has never been observed.)

Subphrenic abscess on the left side, associated with pulmonary abscess, is usually of metastatic origin. In 1 of our cases it followed perforation of an abscess of the spleen; in another, perforation of an abscess in the left lobe of the liver. We have never seen it result from transdiaphragmatic extension from the lung, although 2 cases of this type have been reported by others. When other metastatic foci are present—e. g., in the brain, skin, kidneys or extremities—together with the clinical evidences of pylephlebitis in a case of pulmonary abscess, one may assume the existence of gangrenous thrombophlebitis of one of the large branches of the pulmonary vein as the source.

DISCUSSION

SOLOMON WEINTRAUB: I have brought the specimens from the cases mentioned by Drs. Antopol and Rabin. In one of these cases the specimens show a pulmonary abscess with pulmonary thrombophlebitis and an abscess in the interventricular septum of the heart. This is the case of a colored man, 22 years of

age, who was admitted to Harlem Hospital complaining of abdominal pain, vomiting, tenderness in the abdomen and productive cough. The patient lived about five days, during which time the question arose whether the condition was a beginning lobar pneumonia, because of the productive cough and chills and fever. Roentgenograms were taken which showed the condition clearly. A flat plate was taken to rule out a ruptured gastric ulcer; the diaphragm was rather high on the left with a rather low splenic flexure, indicating that there was something present which pushed the left side of the diaphragm up and the splenic flexure down. The roentgenogram of the lung revealed a definite level of fluid. At autopsy the patient showed, in addition to the pulmonary abscess, pulmonary phlebitis, as shown in the specimen, 2 abscesses of the interventricular septum, infarcts of the liver and left kidney and ruptured infarcts of the spleen with a left subdiaphragmatic abscess. There was phlebitis of the splenic vein, which explained the abscesses in the liver.

PAUL W. ASCHNER: My interest in this subject was aroused several years ago from the clinical standpoint, and later from the pathologic standpoint (*Ann. Surg.* **86**:41, 1927). About 1918, during the epidemic of influenza, I had charge of all the patients with empyema at Mount Sinai Hospital and was impressed by a number of embolic complications that occurred in this group. I was surprised that abscess of the brain was practically the only embolic phenomenon associated with pulmonary suppuration that was reported in the literature. I collected a number of instances of embolic and metastatic infections in other organs which were secondary to pulmonary suppuration. It seemed that there must be a pathologic basis for these lesions. In other words, the pulmonary abscess itself could not account for the frequency of abscess of the brain unless there was a secondary thrombophlebitis of the pulmonary veins. In going over the records of postmortem examinations in about 98 cases, I discovered evidence in 12 of these instances that lesions of the pulmonary vein were the cause of embolic phenomena. The reason that the condition affects the left side of the brain more frequently is probably purely mechanical. The infective material thrown off by the thrombophlebitis in the pulmonary vein enters the left auricle and then the ventricle and is expelled through the aorta. The left common carotid artery, arising directly from the aorta, seems in most direct line with the blood stream of the latter. There were, however, not only lesions in the brain but renal abscesses, splenic infarcts and lesions of the bones and joints.

The terminology is somewhat loose. One speaks of embolic and metastatic abscesses interchangeably, which leads to confusion, although the distinction is one of degree. A typical metastatic abscess is the one encountered in the renal parenchyma. The primary lesion is a minute one in the skin, a furuncle, and a few organisms get into the circulation without any gross venous involvement. If there were gross venous involvement, the result would not be just one abscess in the kidney. There would be repeated feeding of infectious emboli into the blood stream and repeated embolic abscesses. That is, by the term "metastatic abscess," one indicates that a few organisms have filtered off into the blood stream and set up a single focus. When gross thrombophlebitis exists, one should speak of embolic abscesses, because infected thrombotic masses are thrown off. When a splenic abscess affects the portal system, that is again an embolic process, because there is usually not an extension of the lesion along the wall of the vein all the way from the spleen to the liver but a splenic thrombophlebitic process in which masses are thrown off and are carried into the liver, again by embolism.

I think that the importance of these studies is to show the value of clinical observation followed by a resort to postmortem material to find the explanation.

PAUL KLEMPERER: A point of importance was brought out in some of these cases. I think that the so-called cryptogenic sepsis in some patients might be explained if one always looked for changes in the pulmonary veins. I distinctly remember 2 cases in which the sepsis could not have been explained if it had not been that a thrombophlebitis of the pulmonary vein was found.

C. B. RABIN: To me just those cases which Dr. Klemperer spoke about are the most interesting—those in which there is a history of sore throat and cough and the condition is considered grip clinically, but in which chills and embolic phenomena develop while the patient is under observation. In both of the cases reported there were the signs and clinical symptoms of sepsis, and a blood culture showed Streptococcus haemolyticus. The nature of the cases was obscure clinically, but it need not have been had the possibility of phlebitis of the pulmonary vein in association with the pulmonary lesion been given consideration. Small lesions occur in the lung in grip or influenza which may give no physical signs. However, roentgen examination in each of these cases showed a pneumonic process of moderate extent. This finding, together with the presence of Streptococcus haemolyticus in the blood culture, in the absence of any further obvious focus, could have led to the proper diagnosis.

I wish to say a word concerning operations on the lungs, especially in the suppurative diseases. Surgeons now have no hesitancy in cutting into the substance of the lung; they have no fear of hemorrhage, and they feel that cutting into a lung is just like cutting into any other tissue. In most respects, this point of view is correct, yet cutting into a pulmonary vein which leads to the left side of the heart incurs the danger of allowing bacteria as well as air to enter the circulation. The danger of washing bacteria from a pulmonary abscess or a bronchiectatic cavity into the circulation is practical as well as theoretical. It appears to me that to prevent this dangerous complication surgeons should use, instead of the scalpel, the cautery, which will seal off the pulmonary vessels and prevent the entrance into the pulmonary veins of infective material.

The concept of Nathan, who belongs to the Schottmüller school, is that the most important mechanism for the maintenance of a constant invasion of the blood stream, which is what is meant by sepsis, is involvement of the pulmonary veins as a secondary focus. He gives the impression that, given a focus somewhere in the body, there would be no sepsis if there were not at the same time secondary involvement of the pulmonary veins. I must take exception to this rather revolutionary view. I am sure that those who have observed cases clinically have seen any number in which there was a focus somewhere in the body that gave rise to a generalized sepsis and in which there was no demonstrable involvement of the lung either clinically or on roentgen examination. The metastatic abscesses are always visualized roentgenologically, if so examined. Yet there are many cases, especially in the early phases of infection, in which the pulmonary substance is not involved, and in which, therefore, there is no infection of the pulmonary veins. One must also bear in mind that although infection of the microscopic vessels of the lung may give rise to metastatic phenomena in various parts of the body, it is not to be considered a cause for sepsis. These small vessels are thrombosed very early. Occasionally bacteria or a clump of bacteria may pass through them into the greater circulation, but it is only when the large vessels are involved that sepsis or generalized infection really takes place.

Regular Meeting, April 27, 1933

PAUL KLEMPERER, *President, Presiding*

TRICUSPID STENOSIS ASSOCIATED WITH CHYLOUS ASCITES. DAVID PERLA.

A woman, aged 48, with a history of rheumatic polyarthritis five years prior to admission and repeated attacks of congestive failure during the past three and a half years, was admitted to the hospital complaining of dyspnea, orthopnea and swelling of the abdomen.

On examination the patient was found to be obese, cyanotic and dyspneic. There was marked engorgement of the veins of the neck. The heart was

moderately enlarged, with evidence of mitral and aortic valvular disease and auricular fibrillation. The liver was large, hard and nonpulsating; ascites was present. There was edema of the lower extremities. A large amount of milky fluid was aspirated from the abdominal cavity. The total fat content of this fluid was 0.24 per cent. The patient had to be tapped every three days. The cyanosis increased. A chill and high fever developed, followed by stupor and death, six months after admission.

At autopsy healed rheumatic lesions of the aortic and tricuspid valves with mitral stenosis and tricuspid stenosis were found. The right auricle was enormously distended. The pericardium was distended with clear serous fluid. There was evidence of chronic passive congestion of the viscera. The abdominal cavity contained 3 liters of milky fluid. It is suggested that the marked venous tension in the left subclavian vein due to the tricuspid stenosis prevented the flow of lymph from the thoracic duct into the vein with consequent obstruction and chylous ascites.

Subacute Bacterial Endocarditis with Rupture of the Superior Mesenteric Artery and Fatal Hemorrhage. David Perla.

Since June, 1931, a man, aged 34, with no antecedent rheumatic history, had had repeated attacks of stinging pain in the finger tips, toes and palms, associated with tender red areas that subsided in from a few hours to a few days. In October, a left hemiplegia developed from which the patient gradually recovered. Since that time he had complained of fever, weakness and sweating. In August, 1932, enlargement of the spleen was first noted.

On examination he was found to have the signs and symptoms of subacute bacterial endocarditis with cardiac hypertrophy, mitral stenosis and insufficiency, aortic insufficiency and enlargement of the liver and spleen. There was secondary anemia. The urine contained albumin and red blood cells. The case ran a septic course for a period of three months. In April, 1933, the patient complained of mild diffuse abdominal cramps. There was no blood in the stools. On April 14 he suddenly went into collapse and died.

At autopsy the following lesions were found: subacute bacterial endocarditis of the aortic and mitral valves, aortic insufficiency, healed rheumatic endocarditis of the aortic valve, multiple healed infarcts of the spleen and kidneys and acute embolic glomerulonephritis. There was also a mycotic aneurysm of the superior mesenteric artery with rupture and hemorrhage into the peritoneum and mesentery. The peritoneal cavity contained 1,700 cc. of partly clotted blood. The mesentery was markedly thickened and dark purplish. There was an extensive hemorrhage dissecting the layers of the mesentery and producing marked edema of the ascending and transverse colon.

Lymphosarcoma of the Second Portion of the Duodenum Without Jaundice. David Perla.

A man, aged 51, was admitted to the hospital complaining of loss of weight, vomiting after meals, weakness and abdominal pain of five months' duration.

Examination revealed a movable tender mass in the epigastrium, the size of an orange, and enlarged cervical, axillary and inguinal lymph nodes. There was secondary anemia. Two years previous to admission the patient noticed lumps in the left side of the neck, which decreased in size under roentgenotherapy, but later reappeared. The stools were positive for blood. Roentgen examination revealed an obstruction in the distal duodenum, causing delayed gastric emptying. The patient continued to vomit, became emaciated and died, three weeks after admission.

At autopsy a large lymphosarcoma was found in the second portion of the duodenum, encircling the wall, with ulceration within the lumen. It compressed the head of the pancreas without invasion and circled the papilla of Vater and the common bile duct, but did not produce obstruction. There was no jaundice.

Metastases were present in both kidneys, and in the cervical, axillary, inguinal and retroperitoneal lymph nodes.

CARCINOMATOUS THROMBO-ENDARTERITIS OF THE PULMONARY VESSELS. E. B. GREENSPAN.

While the etiology of certain types of obliterative endarteritis of the pulmonary vessels is not clear, there is one type in which the pathogenesis is known. In this group, the intimal proliferation is the direct result of neoplastic invasion of the lung, and the presence of the obliterating endarteritis causes a generalized narrowing of the pulmonary arterioles and the smaller arteries, right ventricular hypertrophy and finally right ventricular cardiac failure.

Four cases were studied, two of which clinically presented the features characteristic of failure of the right ventricle. In the third case, the symptoms were entirely gastro-intestinal, except for sudden cardiac collapse, in which the patient died. In the fourth case, the abdominal symptoms were associated with progressively increasing dyspnea.

At autopsy the first three cases mentioned revealed a scirrhous adenocarcinoma of the stomach. The primary tumor in the fourth case was an adenocarcinoma of the sigmoid colon. At necropsy in all four cases the pulmonary hilar lymph nodes were moderately enlarged by metastases, and the pleura revealed an interlacing grayish-white network of lymph channels filled with tumor cells which appeared to spread out from the pulmonary hilus. Many pinpoint to pinhead sized nodules were found within the parenchyma of the lung.

Of the four cases presented, only one conforms with the picture of pure lymphatic dissemination that has been stressed by certain French writers. In this case metastases from a sigmoid adenocarcinoma greatly enlarged the mediastinal lymph nodes and caused a definite carcinomatous lymphangitis of the lungs without any vascular alterations. In the remaining three cases, the presence of tumor cells in the perivascular lymphatics called forth a marked increase in the adventitial tissue and an intimal fibrous hyperplasia in many of the smaller arteries and the arterioles. Varying degrees of arterial obliteration were produced, often with complete closure of the lumen. In part the intimal response may be ascribed to invasion of the adventitia and the media by scirrhous carcinoma. In other arteries, even after serial sections had been made, no such invasion was found, and the intimal response may in part have been the result of some humoral or direct mechanical stimulus exerted by the presence of tumor cells in the lymphatic channels.

Additional cause for the narrowing of the pulmonary arterial bed was seen in the apposition of a platelet thrombus or of carcinoma cells on a hyperplastic intima, which resulted in either a partial or a total obliteration of the vessel.

In this study the findings would indicate that the obliterating endarteritis was mainly the result of lymphangitis carcinomatosa and not, as M. B. Schmidt believed, principally the result of multiple carcinomatous embolization to the pulmonary arteries.

AORTIC STENOSIS: A DIFFERENTIAL STUDY BETWEEN CALCIFIED BICUSPID VALVES OF CONGENITAL AND INFLAMMATORY ORIGIN. MAX TRUBEK and LOUIS F. BISHOP, JR.

MAX TRUBEK: Most cases of aortic stenosis may be etiologically grouped into three classes: 1. Cases of infectious origin, including those of true rheumatism, other types of infection with "rheumatic" changes and healed bacterial endocarditis. 2. Arteriosclerotic or degenerative lesions without previous inflammation. 3. Congenitally defective cusps with subsequent calcification.

After healing, fusion and calcification, it is often increasingly difficult to decide on gross examination whether one is dealing with an old inflammatory process or with a defective valve of the bicuspid variety with subsequent calcification.

The chief basis for distinction is the relationship of the origin of the annulus fibrosus to the aortic elastic media at the ridge or raphe dividing the conjoint valve.

Mönckeberg (1904) showed the architecture of the aortic cusps and, using differential stains for elastic and connective tissue, described the annulus fibrosus and its changing relationships to the aortic media at the commissures and within the cusps in normal valves. Lewis and Grant (1923) have provided a method for the microscopic identification of a congenital raphe and a fused commissure ridge by serial sections stained for elastic tissue. The contribution of Gross and Kugel (1931) established the normal architecture of each cusp and showed the contiguous relationships so that any cusp can be identified on microscopic section.

Proper reference to Mönckeberg's description of the normal aortic valve has been neglected in recent years. For the first time in such a study he used the Weigert elastica and van Gieson stains. He recognized that as the commissure is approached there is a reversal of the relationships of the annulus fibrosus to the aortic elastic media. The media seems to withdraw inward and the fibrous annulus to advance superficially from beneath the aortic elastica layer, so that at the commissure it lies superficially and extends into the cusp at its fibrous layer. The wedge-shaped junction, at first directed from the left below to the right above, becomes horizontal and then takes the opposite direction at the commissure, from the right below to the left above.

By the method described by Lewis and Grant it was possible to differentiate a congenital raphe or a fused commissure ridge in aortic valves with advanced calcification and stenosis. At the congenital raphe the normal relationships for the center of the cusp are maintained; the reversal does not occur.

In one case the presence of associated cardiovascular anomalies, coarctation of the aorta and patent ductus arteriosus, could not be taken as presumptive evidence for a congenital defect underlying the calcified aortic cusps; microscopic sections through the ridge in the combined cusp showed a fused commissure of inflammatory origin.

In one case of bacterial endocarditis the apparently normal commissural relationship at the raphe, dividing the conjoint cusps, in the absence of any inflammatory reaction and without the characteristic gross appearance of a congenital bicuspid valve, may merely have represented an abortive attempt to form a commissure. This finding and the high position of the raphe would seem to indicate a relatively later arrest in the development from the bulbus cordis thickening than occurs in the low, smooth raphe which can satisfactorily be identified on gross examination.

Louis F. Bishop, Jr.: One of the first recorded observations on the differential study of bicuspid aortic valves was that of Paget (1844), who wrote: ". . . in the majority of cases in which only two valves have been found in the aorta or pulmonary artery, those valves have been diseased, and often extremely diseased."

Thomas Peacock (1853) in his book, "Malformations of the Human Heart," wrote as follows: "In by far the most frequent form of malformation of the semilunar valves there are two segments, and the deficiency is apparently due to the adhesion of the contiguous sides of two of the original three valves and the atrophy of the corresponding angle of attachment."

Sir William Osler has stated the gross criteria for distinguishing the bicuspid valve of congenital origin: "The free border was usually straight, oftentimes curled, and in no instance was there any nodular thickening indicative of corpus Arantii. The attached border presented, from the ventricular aspect, either the normal contour of a semilunar valve, or, more commonly, a shallow groove, indicative of the junction of two cusps. The aortic side of the valve presented in all the cases a more or less distinct raphe, dividing or indicating a division into two sinuses. The sinuses of Valsalva, thus incompletely marked, were usually of equal size." These gross criteria are exceedingly important and can be used in the majority of cases.

There are some cases, as shown in this study, in which these gross criteria are decidedly insufficient. The difficulty in deciding this point in one case of advanced aortic stenosis with an apparently bicuspid valve led me to take this specimen to Dr. Maude E. Abbott in Montreal. She told me that a histologic study of these cases was necessary and stimulated us to do this work. This has been done by Lewis and Grant in a series of cases of bacterial endocarditis. At the present time, this is as far as one can go in the differential study.

THE USE, SIGNIFICANCE AND INTERPRETATION OF SILVER IMPREGNATIONS IN PATHOLOGY. NATHAN CHANDLER ROOT.

Silver impregnation is not a formidable laboratory method, and successful impregnations may be carried out by a college sophomore without any previous training if directions are carefully followed. The method has been slow in gaining ground in general use, owing to the fondness of pathologists for the simpler, hematoxylin-eosin technic or similar stains. Although Ranvier instituted silver impregnation in the early sixties, it was not till 1900, when Bielschowsky and Simarro began working with ammoniacal silver impregnations, that the technic began to develop. Since that time Bielschowsky and Ramon y Cajal and their followers have devised many methods for as many purposes. The fact that blocks of tissue or frozen sections were alone available held back progress, but Maresch and his successors gradually perfected methods in which paraffin sections gave good results in all but nerve tissue, and even that is now yielding to treatment, although the results are as yet not entirely successful.

The chemistry of the technic depends on attaching silver ions to certain "silver centers" in fixed tissue and then developing these with a reducing agent so that the silver is rendered black. Most methods replace the silver with gold, by means of gold chloride, which may be intensified by the Laidlaw method, using oxalic acid or a combination of this with formaldehyde. The exact chemistry of the technic is poorly understood, for nothing is known about the "silver centers." It is doubtful if they are very similar to the subsalts produced by exposure to light in the photographic plate, although the analogy has often been stressed. There are two general groups of silver salts used in impregnations: silver nitrate, which requires a strong reducer to develop it, and silver diamino salts, which are readily reduced by formaldehyde. The color effects in silver impregnation and the tissue components that become impregnated depend on: (*a*) the fixation used; (*b*) the pretreatment with alkaline or acid baths, mordants, etc.; (*c*) the type of silver solution used; (*d*) the type of toning employed, and (*e*) the use or omission of intensification.

Silver impregnation may be used as a general, routine stain; it brings out differences in connective tissue and bone, striae in skeletal muscle, certain micro-organisms (Leishmania), spermatozoa and other delicate structures, such as mitotic figures. It may be specifically used for micro-organisms, connective tissue (reticulum especially), various components of the nervous system (neurites, neuroglia, etc.), specific argentaffin granules or other granules, such as melanin, certain lipins and lime salts.

Interpretation depends on familiarity with the results of given methods of impregnation, and must be worked out by experience; there is no short cut to interpreting all impregnations. The acquisition of such experience is not a difficult matter, however, and may be materially hastened by the use of and comparison with other familiar stains.

Cleanliness in the technic is a prime factor for success, and the use of distilled water is almost invariably indicated, unless specifically contraindicated in the directions for impregnation. In those methods in which good and bad results occur in the same group of sections, it is well to make enough sections at a time to insure a reasonably large number of satisfactory slides; this refers chiefly to work on frozen sections of the central nervous system, which is notoriously capricious. When using most of the impregnations designed to bring out connective tissue or

muscle striae or general impregnations, the results are constant and usually satisfactory. The technic can be used in a routine way, just as one employs the old-fashioned hematoxylin-eosin method.

DISCUSSION

GEORGE F. LAIDLAW: Dr. Foot has long been a crusader for the use of silver in the pathologic laboratory, and I wish him all success. I am glad to acknowledge the benefit that I myself have derived from Dr. Foot's writings. Silver is one of the most remarkable of histologic reagents. There are probably four or five histologists in this city using silver, and there ought to be forty. Throughout the country there are perhaps forty using it, and there should be four hundred. In our own work we have formulated certain principles. The first is that the fixative determines the result. If one uses the right fixative, one can stain specifically any desired part of the tissue. One can stain the basic substance and leave the cells out, or stain the cells and leave the basic substance out; or one can stain the cell bodies and not the nuclei, or stain the nuclei and not the cell bodies. It is all determined by the fixing fluid.

Another thing that we have learned is that long silver technics are dirty. For neurites we follow the Gros-Bielschowsky method, and we have cut the time down to two minutes. Frozen sections are put in silver nitrate for two minutes, in formaldehyde for two minutes and in ammoniacal silver for two minutes, making six minutes in all.

Dr. Foot spoke of the liberal use of distilled water between the steps. This may apply to some technics, but in staining neurites by the Gros-Bielschowsky method we fear distilled water as the devil fears holy water. We believe that water extracts something from the tissue that is essential to the reaction. We even hesitate to renew the formaldehyde solution in which the tissue was fixed, fearing to lose something important. When we cut the sections, we drop them back into the same formaldehyde in which the tissue was fixed, and leave them there until ready for staining. Between the formaldehyde and the silver nitrate, we rinse the sections in distilled water for the shortest time possible, a few seconds only, so that they carry some formaldehyde over into the nitrate. Then we rinse them no more. The sections carry the silver nitrate over into the reducing formaldehyde, and some of the reducing formaldehyde over into the ammoniacal silver. I have tried mixing the three fluids together, but this did not work well. Cajal advised dropping some nitrate into the reducing formaldehyde to make the nerve fibers come out blacker.

One could discuss this subject for a long time without exhausting it. I believe that the distinguished author of the paper will agree with me that the surface of silver staining has scarcely been scratched and that there is no more fruitful field today for the ambitious young pathologist than the study of silver staining in pathologic histology.

ALFRED PLAUT: I should like to ask Dr. Foot a question. When one has a formaldehyde-fixed tumor and one is doubtful whether to call it carcinoma or sarcoma, what silver method should one apply for differentiation?

PAUL KLEMPERER: I should like to ask if Dr. Foot has succeeded in impregnating the basement membrane of the glomeruli of the kidney. Dr. Foot has just touched on his controversy with Mallory and Parker in regard to the differences between the reticulum fibers and collagen fibers. I wonder if he would not give his present point of view. This question is of considerable theoretical importance, and also, as Dr. Plaut has mentioned, it is of practical value in the recognition of the very early developmental stages in certain tumors, particularly in the question of reticulum cell sarcoma and lymphosarcoma.

IRVING GRAEF: I should like to ask if the silver stains have been reliable enough for the specific identification of fibrinoid degeneration of collagen. The use of the Gram-Weigert technic has always been limited because of precipitation of dye, and we have found that the p_H of the fixing fluids in general laboratory

use is extremely variable and makes the Mallory phosphotungstic acid-hematoxylin method variable in its results. We have tried to use one of Dr. Foot's variants of the silver technic to determine the presence of fibrin in collagen, and have found it fairly successful, but have always had to check it up with the Weigert or the phosphotungstic acid-hematoxylin methods. I should like to ask Dr. Foot for more information on the applicability of silver methods in the identification of fibrin or fibrin-like substances.

NATHAN CHANDLER FOOT: I want to thank Dr. Laidlaw for backing me up so nobly in my crusading career, and call to his attention that in connection with the use of distilled water, I said "except when specified." Of course in such methods as that of Rogers it is suicidal to use any distilled water between the formaldehyde and the impregnating solution, but I was thinking in more general terms when I mentioned the value of distilled water between the steps; for instance, in impregnation of connective tissue it is imperative to get clean results.

Another point which Dr. Laidlaw brought out was the fascinating game of juggling with these things. In using variants of almost the same method, by alternating the different steps of one of these four processes, the steps of fixation and impregnation, and the developing and toning, one can get all sorts of combinations, so that if one method does not work, another will. I do not expect any one, after he becomes expert in the use of silver impregnation, to use any specific method. He will probably use his own.

The surface of the subject is indeed only scratched, and I do not think that we can make our scratches much deeper until we can get a little further along in the chemistry of the technic and understand more clearly what we are doing. There are a great many of the steps in our work which we do not know about, and if we could only get to understand them, it would make a great difference.

In reply to Dr. Plaut's question, the differentiation between sarcoma and carcinoma, I have found this as a general rule satisfactory with silver methods, in that the reticulum of the stroma of a carcinoma usually stops in a wall at the basement membrane, or it is only in those parts of the slide where the carcinoma cells have become broken up that the reticulum penetrates. On the other hand, in reticulo-endothelial sarcomas a dense network of reticulum fibers runs all through the tumor. I have demonstrated that certain tumors which were supposed to be carcinomatous—one case in the thyroid I am thinking of especially—were really reticulo-endothelial in origin, because of this dense network, which ran through and among all the cells. One may see other tumors which one is sure are reticulo-endothelial, but in which one cannot demonstrate any reticulum; in this difficulty, one is thrown back on another hypothesis—that the tumor may be muscular or neurogenic—and then other methods of staining must be used.

I was asked which method we use for connective tissue; I shall have to be immodest and say that we use the "Foot and Foot" method, which my daughter and I worked out. We have a number of variants, but time prevents my giving all the steps. I shall be glad to send an outline of the particular method we use to any one who wishes it; unfortunately our reprints are exhausted.

In reply to Dr. Klemperer's question concerning the glomeruli of the kidney, we can demonstrate the capsule of the glomeruli, but interestingly and amusingly, we can seldom if ever demonstrate any reticulum in the glomerulus itself. Once in a while, particularly in rabbits, we may demonstrate it, but in human tissue it seldom comes out.

In regard to the question about reticulin and collagen, that, after all, is a matter of hair-splitting. It seems to me that reticulin and collagen are intimately related, but there may be some slight chemical difference between the two, as was thought by Siegfried, who did the original analytic work. He found a different empirical formula for the two substances. On impregnation with silver under certain conditions, one can see reticulin as a black substance and collagen as a red one, and then one may find them overlapping or running into one another. Reticulin or collagen may therefore be a form of coating on some indifferent sort of a fiber. There are numerous indifferent fibers in the body which one cannot

impregnate. I have noticed this in several instances, and it is possible that collagen and reticulin may be either a coating or a substance which fills the fiber, like starch in linen. The substances are sufficiently different from each other to react differently to silver. In using the method just mentioned for general impregnation, if one employs a tannate variant, collagen and reticulin both come out red; if one does not use it, the reticulin comes out black, whereas the collagen comes out red. I do not think that this proves whether the two are the same or not. My belief that they are different was based on a smelly piece of work that I did a long time ago, in which a number of spleens and lungs were digested with pancreatin, the reticulin was reprecipitated, and an attempt was made to isolate it. I isolated something which assayed very close to the Siegfried formula and which I could impregnate with silver. It was presumably brought down in a series of chemical reactions after the collagen had been removed, and for that reason I thought that it was different from collagen. Guyon and Nageotte attacked my views in a paper that I could not fully comprehend (it was so complicatedly physicochemical that it left me gasping). There was a good deal of talk about differences of interfaces and surface tensions, which would explain the differences in the black and red impregnation.

As to fibrin, I have had practically no success in impregnating fibrin with silver, and for that reason I have always done just what Dr. Graef who asked about it does: I have fallen back on the phosphotungstic acid-hematoxylin or Gram-Weigert stain to demonstrate fibrin.

In working out the development of reticulin in tubercles, it was important to find out whether reticulin developed from the fibrin in the tubercle. By making a series of stains with silver and phosphotungstic acid, I demonstrated that reticulin did not develop from fibrin. Silver methods are worthless for impregnating fibrin.

BUFFALO PATHOLOGICAL SOCIETY

Regular Meeting, April 29, 1933

KORNEL TERPLAN, *President, in the Chair*

PNEUMONIA IN NEW-BORN INFANTS. MARGARET WARWICK.

In a series of 258 consecutive autopsies on infants dying during the first ten days of life or stillborn, 18 were so macerated that satisfactory microscopic sections of the lungs could not be obtained. This left 240 which were examined and analyzed. Forty-six infants, or 19.5 per cent, showed pneumonia. Two of these, however, had atresia of the esophagus, and repeated aspirations of food had caused a massive pneumonia; another was born of a mother who was critically ill with lobar pneumonia. These 3 were therefore omitted, and a study was made of 43, or 17 per cent.

Of these 10 were stillborn, 8 lived less than twelve hours and 6 lived between one and two days. In 24, or 56 per cent, pneumonia must therefore have developed in utero. Also, 2 were of only 5 months' gestation, showing that pneumonia can develop long before birth. About half of the infants, i. e., 20, or 46.5 per cent, had no other pathologic lesions; without microscopic sections, these would be called cases of atelectasis. Twenty-one, or 50 per cent, showed traumatic lesions, and 2, or 4.8 per cent, showed congenital lesions.

Only 11 infants, or 25.6 per cent, were born by spontaneous delivery; in all the other cases there was interference of various kinds. Three infants were delivered by cesarean section, abdominal in 2 cases and vaginal in 1. The series included many abnormal positions. Many of the infants were larger than usual, while a few were very small. These abnormalities of position and delivery sug-

gest that there may have been asphyxia owing to a variety of causes, and this may have caused an aspiration of amniotic fluid which may or may not have been infected with pathogenic organisms.

Amniotic fluid is a frequent finding in the lungs of infants who die during or shortly after birth. Some of the various constituents of amniotic fluid were found in 175, or 73 per cent, of the 240 infants; among the 43 with pneumonia, it was present in 37, or 86 per cent. The material consisted of fat, cornified epithelium, fluid and masses of bile salts in various ratios, and was usually found in the midst of the area showing the exudation of leukocytes.

All the lungs were stained by Gram's method, and in 11 instances, or 25.5 per cent, showed bacteria. There is much difference of opinion about the etiology of pneumonia. The majority of observers think that it is caused by bacteria which have entered the amniotic fluid by some route, usually by premature rupture of the membranes. In only 5, or 12 per cent, of this series did the rupture of the membranes occur long enough before birth to have caused this chain of events. In 63 per cent this period was less than one day; in the others it was not known. Furthermore, the 3 infants delivered by cesarean section could not have been thus infected.

Atelectasis is a frequent accompaniment of pneumonia. While atelectasis is frequently recognized, the underlying pneumonia is not. Many have observed that atelectatic lungs are frequent sites of pneumonia. In this series, there were large areas of atelectasis in 20, or 46.5 per cent, small areas in 11, or 28 per cent, and none in 11, or 25.6 per cent. The foreign material and exudate were frequently found in the center of atelectatic areas.

The majority of observers think that pneumonia in the new-born is caused by bacteria, but the conclusion from this study is that it is frequently, if not always, caused by the chemical or mechanical irritation of the aspirated amniotic fluid. Chemical irritants can cause acute inflammation and exudation in other parts of the body. Winternitz found that pneumonia could be produced by dilute acid, and Pierson by iodized oil. It occurs in cases in which there is no evidence of the entrance of pathogenic organisms. Also, many of these infants had handicaps of various kinds associated with size, position and difficult delivery which may have lowered their resistance and made them easier prey to either bacterial or chemical invasion of the lungs. It is possible that this pneumonia is caused by either bacteria or chemicals or both. At any rate, the pneumonia of new-born infants is a definite entity and should receive more attention from obstetricians and pediatricians. It may cause death directly by exudation or indirectly by preventing proper aeration of the lungs.

MALIGNANT HEPATOMA IN A YOUNG WOMAN. MARGARET WARWICK.

A woman, 20 years of age, was admitted to the Millard Fillmore Hospital on Feb. 19, 1933, complaining of loss of weight and strength and a growing tumor in the abdomen. The illness began in January, 1930, when the patient was pregnant about four months. A cramplike pain in the left upper quadrant of the abdomen was first noted on walking or other exertion. Following delivery the patient never regained her former strength. There was a loss of 30 pounds (13.6 Kg.) in weight. Physical examination revealed distention of the abdomen by a large irregular mass, about the size of a grape-fruit, under the left costal margin. This mass was fixed but not tender or painful. Roentgen examination gave negative results. The hemoglobin content was 55 per cent, the red cell count 3,170,000 and the white blood count 6,450, with 75 per cent neutrophils and 25 per cent lymphocytes. The blood sugar was 100 mg., and the urea nitrogen, 14 mg. The Wassermann reaction was negative. A laparotomy on Feb. 27, 1933, showed a large tumor in the left lobe of the liver, which was increased in size. A diagnosis of malignant hepatoma was made at biopsy. Postoperatively, the patient progressively lost strength and weight. She died on March 1.

At autopsy the liver was found to be greatly enlarged, especially the left lobe (weight, 2,475 Gm.). In the left lobe was a large white tumor mass with numerous areas of necrosis and extravasated blood. This was covered by a thin layer of tissue, so that it was not visible from the anterior surface. Numerous tumor nodules of a similar nature, varying from 1 to 3 cm. in diameter, were present in both lobes. Tributary lymph nodes were greatly enlarged and contained tumor tissue identical with that in the liver. Also present were recent bacterial endocarditis, multiple infarcts of the spleen and a small persistent thymus.

Microscopically, the tumor consisted of large atypical cells with pale vesicular nuclei and numerous mitotic figures. These embryonic cells resembled liver cells with typical cord formation. Large areas of necrosis were seen.

MENINGITIS IN A DIABETIC PATIENT: VARIATIONS IN THE COMPOSITION OF THE SPINAL FLUID. ROGER S. HUBBARD and BYRON D. BOWEN.

Specimens of blood and spinal fluid taken simultaneously from a patient with meningitis due to type III pneumococcus, secondary to a chronic infection of the ear, were studied. The first were taken eight hours after the first symptoms of the acute condition were noticed and four hours after coma, nondiabetic in type, developed, and the others at intervals as shown in the table. All showed marked turbidity owing to the large number of cells present. The patient died fourteen hours after the last specimen was obtained.

Determinations on the Blood and Spinal Fluid

		Whole Blood		Spinal Fluid	
Date	Time	Sugar, per Cent	Sodium Chloride, per Cent	Sugar,* per Cent	Sodium Chloride, per Cent
April 17	12 m.	0.368	0.414	0.055	0.648
April 17	4 p.m.	0.256†	.....	0.007	.....
April 19	12 m.	0.740	0.462	0.280	0.688

* These results are corrected for nondextrose reducing substances, determined after short incubation with a high concentration of washed yeast cells.
† Insulin was used during the preceding four hour period.

The results clearly show that dextrose may be present in typical meningitic spinal fluid in amounts roughly parallel to the concentration of sugar in the blood. Since it was proved that some dextrose was found in each specimen of spinal fluid, and therefore that this compound was always present in amounts greater than the organisms and cells could destroy, it seemed legitimate to try to determine approximately the conditions of equilibrium. The ratios between the blood and spinal fluid sugar contained in the literature vary greatly (Peters, J. P., and Van Slyke, D. D.: Quantitative Clinical Chemistry, Baltimore, Williams & Wilkins Co., 1931, vol. 1), and there are no figures available with which glycolysis by a mixture of leukocytes and bacteria such as these fluids presented could be properly compared. Equations containing two unknown quantities were therefore formulated for each of the three experiments, and the probable values for the amount of sugar entering the spinal fluid and for the concentration of that substance removed by glycolysis were calculated on the assumption that both were constant throughout the period of observation. The results of these calculations agreed surprisingly well. The concentration of dextrose exposed to the glycolytic action of the cells appeared to be about 60 per cent of that in the blood, a figure which is lower than that accepted by many authorities, but which is within the range sometimes reported as normal. If this figure is accepted as correct, the calculated concentrations of dextrose destroyed were 0.166 per cent in the first experiment, 0.147 per cent in the second and 0.165 per cent in the third. Since there were a number of important factors which could not be adequately controlled—the constancy of the enzymatic potency of the cell suspension and the rate of variation of the concentration of blood sugar, for example—great emphasis cannot be laid on the particular values obtained.

The results, however, justify the statement that the dextrose in meningitic spinal fluid is controlled by definite factors, and that one of these factors is the concentration of sugar in the blood. The chloride in the spinal fluid showed a similar parallelism to the concentration in the blood. In the first sample this was 1.57 and in the last one 1.49 times as concentrated as in specimens of blood drawn simultaneously. The blood chloride was therefore an important factor in determining the concentration of chloride in the spinal fluid of this patient.

PRIMARY PULMONARY TUBERCULOUS FOCI WITHOUT CHANGES IN THE LYMPH NODES. K. TERPLAN and E. C. KOENIG.

When Kuess first described the primary tuberculous focus in children, he stated that the lymph nodes regional to the focus are always involved, sometimes to a degree altogether out of proportion to the extent of the primary lesion. In a general way Ghon confirmed Kuess' observation. Little is known concerning primary foci showing no tuberculous lesions in the lymph nodes which drain them.

Ghon was impressed by one of his cases, that of a girl, aged 5½ years, in which he could not find gross tuberculous lesions in the regional lymph nodes. In 1930 Ghon and Kudlich reported two similar cases, the first in a girl 13 years old and the second in a woman 32 years old. Serial sections from the regional lymph nodes in these two cases did not reveal any tuberculous lesions. Blumenberg also reported two instances of primary tuberculous foci with an absence of gross changes in the lymph nodes. Ghon, however, thought that the cases of Blumenberg were not convincing. In considering his own material Ghon pointed out that a small intrapulmonary node may have been overlooked grossly. Further, he suggested that special attention should be directed toward unusual cases of primary tuberculous infection without changes in the lymph nodes.

During the past six months two older children were examined who showed primary tuberculous foci in the lungs but no demonstrable lesions in the regional lymph nodes. Both of these patients gave negative tuberculin tests during life. Roentgenographic examinations of the lungs were made post mortem.

The first patient, a boy aged 12 years, dying of an abscess of the brain, showed a typical primary healed focus in the right lower lobe with a calcified nucleus on the border of which there was beginning metaplastic bone formation. A so-called specific capsule was present. The whole structure was surrounded by normal lung tissue. This focus was first discovered by means of roentgen rays. All the regional lymph nodes were examined in serial sections. With the exception of a small thickening of the reticulum in the regional lymph node of the pulmonary ligament, which was not nodular and therefore could hardly be interpreted as a healed tubercle, no tuberculous lesions were found in the lymph nodes.

The second patient, a girl aged 15 years, dying of uremia from chronic nephritis, presented a primary focus in the left upper lobe that had already been seen and felt grossly. Histologically, this focus differed from the one in the first case only in that bone formation had not yet taken place. Serial sections through all the regional lymph nodes were completely negative for tuberculosis.

In both cases thorough examination of other organs revealed no extrapulmonary tuberculosis. The age of the primary foci could not be determined with certainty.

The foregoing cases are reported for several reasons. First, they are the only cases of primary tuberculous foci in lungs with no changes in the lymph nodes in which tuberculin tests were performed during life and in which postmortem roentgen examination was made. Further, it is stressed that in adolescent children with no tuberculous changes in the lymph nodes thorough gross examination of the lungs themselves and postmortem roentgen examination are mandatory before a negative diagnosis of primary tuberculosis can be made. By this procedure additional cases of primary tuberculous foci without "complex" lymph node changes may perhaps be discovered. Finally, these cases suggest that primary tuberculous infection in late childhood, when, in general, the resistance is good, may restrict itself in rare cases to the lung tissue. Of course, the number of infecting organ-

isms may also be an important factor. It must be pointed out, however, that the two primary foci observed were not smaller than those seen in many other cases of typical changes in the regional lymph nodes.

A Tension Cavity in Primary Pulmonary Tuberculosis in an Infant. K. Terplan, F. Kenny and S. Sanes.

The term "primary cavity" was applied to cavity formation in primary focal lesions in tuberculosis. According to Ghon's estimates small cavities are not rare. Cheesy foci the size of a hen's egg which have become sequestrated and then converted into cavities are occasionally described. Exceptionally rare, however, are primary cavities in which a whole lobe is involved.

Ghon pointed out that most primary cavities have a clean wall which is sometimes rather thin. Large cavities in huge foci often show irregular borders, their walls consisting of necrotic material. Heretofore no attention has been called to a gradually increasing content of air in a cavity under certain conditions.

A colored boy, aged 10 months, died after an illness consisting of fever, vomiting and loss of weight of three months' duration. There was no tuberculosis in the family. Physical examination revealed a colored boy, fairly well developed. The frontal bosses were prominent. The cervical, axillary and inguinal nodes were palpable. A rachitic rosary was present. The right side of the chest in its lower two thirds was tympanitic. Here breath sounds were sometimes entirely absent, at other times merely suppressed. The upper right and entire left portions of the chest showed puerile breathing with many râles and rhonchi. The fingers and toes were moderately clubbed. Roentgen examination of the chest revealed areas of consolidation in both lungs resembling those of pneumonia. In the right side of the chest there was a large irregular translucent area which possessed the appearance of loops of large intestine. Barium given by mouth and colon, however, caused no filling. The Mantoux test gave negative results. The spinal fluid showed 3 cells.

This case is presented because it showed at autopsy a huge primary cavity (5.5 by 7.5 cm. in diameter) of almost the entire right lower lobe of the lung, with practically complete disappearance of the pulmonary parenchyma, but with preservation of the greater part of the bronchial tree. The right upper and middle lobes showed compression atelectasis. The mediastinum was displaced to the left. In addition, the left upper and lower lobes showed tuberculous cheesy bronchopneumonia. Small tubercles were found in the spleen and recent tuberculous erosions in Peyer's patches in the lower ileum. The right tracheobronchial and paratracheal lymph nodes were caseous, and showed on section cheesy cavities. Smears of content revealed thousands of tubercle bacilli.

A main bronchus of the second order opened into the cavity for a short distance; its peripheral extension had been entirely "melted away." The lumen of the preserved bronchus was almost totally filled with cheesy material. The cavity was markedly distended with air. Its wall and the bronchovascular framework were covered with a friable cheesy exudate. This condition, to which the term "tension pneumocavern" seems applicable, can then be explained as the result of an obstructive "valvular" action by the bronchial content. The active efforts of inspiration forced air into the cavity against the partially obstructing exudate. The passive movements of expiration were not powerful enough to force air out. Further, with destruction of pulmonary parenchyma the lower lobe had lost its elasticity. Finally, the right lower lobe was fixed to the parietal pleura by firm fibrinous adhesions.

It is interesting to note that the child did not die of acute miliary tuberculosis, but of extensive tuberculous involvement of both lungs. In other words, the course of primary tuberculosis in this case was similar to that of severe progressive pulmonary tuberculosis in adults. Only the spleen showed hematogenous tubercles; the liver and kidneys were free in examined sections. The question was raised as to the occurrence of similar tension cavities of the lungs in progressive cheesy tuberculosis of adults following partial valvelike occlusion of the bronchi.

Book Reviews

Die Lokalisationstendenz bei Metastasierung durch die Venen in der Leber. By Erik Karlmark, Acta pathologica et microbiologica Scandinavica, Supplementum XIII. Pp. 203. Copenhagen: Levin & Munksgaard, 1932.

Karlmark published a study in *Hygiea* in 1926 and one in *Anatomischer Anzeiger* in 1927. Both deal with resorption from the gallbladder and the way it fills; the second also discusses the normal valves of the bile passages. Although these studies undoubtedly stimulated the present investigation, its chief impetus was apparently from curiosity regarding the location of secondary growths in the liver resulting from sarcoma of the gallbladder. From a few such tumors that the author was able to examine and from competent reports by others he noted that the hepatic metastases were chiefly in the quadrate lobe. This observation naturally was followed by questions concerning the normal course of the veins draining the gallbladder and the extrahepatic bile ducts. Study of these veins constitutes the main theme of the monograph. Ture Petrén worked with Karlmark in demonstrating their normal anatomy. Of seventy injections into the veins of the biliary apparatus, the results of fifty-one provided material suitable for examination. The course of the veins from the gallbladder and bile ducts was charted for each of the successful preparations. The preparations were studied stereoscopically, roentgenoscopically and by reconstruction models. Translucent preparations were made after the methods of Spalteholz and others consisted simply of the veins into which pyroxilin (celloidin) was injected with the intervening tissue removed by digestion.

The usual accounts in the literature of a discharge of blood from the veins of the gallbladder and bile ducts directly into the main trunk of the portal vein or into one of its main branches were found to have no basis. Indeed, the conditions found by Karlmark and Petrén are quite remarkable, for after the venous blood is collected from the gallbladder and its ducts by minute vessels which join so as to form veins of considerable size, these larger trunks pass into the liver where they split into fine branches which empty into small radicles of the hepatic veins. There are consequently retia mirabilia both distally and proximally for these veins, a state of affairs comparable with the efferent arteries of the renal glomeruli, which also begin and end in capillaries. Actual union between the veins of the biliary apparatus and any portions of the portal system was found so rarely that it was regarded as an anomaly.

The number, location and course of the veins of the hepatic, cystic and common bile ducts and of the veins from the neck and the fundus of the gallbladder are described and illustrated. Names are suggested for many of the veins. A substantial portion of the value of the monograph is in the twenty beautiful full page illustrations of the veins and of a few types of disease, sarcomas of the gallbladder, for example, for which the anatomy of the biliary veins has important relations. There are also many tables in which is scheduled information concerning these forms of disease. The table for sarcomas of the gallbladder includes details of thirty tumors. Unusual consideration is shown in explaining why reports of twelve such tumors were not thought worthy of inclusion with the thirty, for each of the twelve reports is reviewed in detail with reasons for its omission. Following the table is a good résumé of the clinical and anatomic features of such neoplasms. But the relation of the venous drainage of the gallbladder and its ducts was found just as directly applicable to acute cholecystitis as to sarcomas of the gallbladder, for the abscesses in the liver secondary to cholecystitis are also found in the quadrate lobe where these veins break up and empty their blood into currents destined for the hepatic veins. These matters are also displayed in a table of thirty-two cases of postcholecystitic hepatic abscesses.

Perhaps the construction of similar tables for carcinomas primary in the gallbladder or its ducts, for hepatic abscesses that follow acute inflammation of the appendix or other places in the gastro-intestinal tract and for tumors in the liver secondary to growths primary in the spleen may be regarded as a "control experiment," for in none of these types of disease is there evidence of important relations to the biliary veins comparable to that which determines the location of lesions in the liver following acute cholecystitis or sarcomas of the gallbladder. The monograph is impressive. Indications of deliberate study, prudent conclusions and thoroughness are conspicuous everywhere. For example, in order to obtain details of one of the reports of a sarcoma of the gallbladder, a report by Cascino ultimately discarded as worthless, Karlmark personally searched the medical libraries of Parma, Pavia and Milan. Material or other aid was obtained from most of the Scandinavian institutes of pathology and from those in many other places in Europe. Among these Lemberg, Strasbourg, Vienna, Berlin, Karlsruhe, Leningrad, Parma, Göttingen, Rome and Heidelberg are mentioned. It was essential that the author have help because of the rarity of some of the diseases under examination for possibilities of relevancy to the disposition of the biliary veins.

It seems that abscesses in the liver due to appendicitis are prone to develop superficially in the dome of the right lobe or in its lateral portions and that hepatic tumors secondary to primary growths in the spleen are located chiefly in the left lobe of the liver. Calculi lodged in the neck or ducts of the gallbladder so hamper the normal flow of blood through some of the biliary veins that surgeons encounter severe bleeding when the stones are removed. Since some of the veins from the fundus of the gallbladder pass directly into the liver and, according to the discoveries announced by Karlmark, empty in hepatic veins, it is not unlikely that the postcholecystectomy bleeding which sometimes fills the abdomen and causes death may be a reversal of the current, so that blood from the liver passes into the peritoneal cavity instead of the inferior vena cava. It is indeed too early to attempt any enumeration of the modifications of present views which are likely to occur as a result of these new conceptions of the venous drainage from the gallbladder and its ducts. However, it seems safe to predict that the work will be widely read and frequently mentioned.

Manual of Veterinary Bacteriology. By Raymond A. Kelser, D.V.M., A.M., Ph.D., Major Veterinary Corps, United States Army; Officer in Charge, Veterinary Division, U. S. Army School; Member of Staff, Pathological Division, Bureau of Animal Industry, U. S. Dept. of Agriculture. Second edition. Cloth. Price, $5.50. Pp. 524, with 93 figures. Baltimore: Williams & Wilkins Company, 1933.

This book contains a large amount of information about veterinary microbiology. "No consideration has been given to organisms not of interest in veterinary medicine." The book is divided into twelve parts. The first part discusses bacteria, their morphology, physiology and classification. The classification is that of the committee of the Society of American Bacteriologists. Part II consists of five chapters on bacteriologic methods. The third part deals with infection and immunity. The chapter on theories of infection and immunity is limited to a brief presentation of the phagocytic and humoral views, Ehrlich's hypothesis of antibody formation and action and Wright's opsonic index. Not a single reference is made to American work in this chapter. Part IV, on bacterial variation, is written by Major James S. Simmons, U. S. Army, who concludes his instructive review as follows: "From this brief discussion, it will be apparent that the bacterial dissociation covers a very broad and intricate field. While there is nothing in this newer knowledge to invalidate bacterial specificity, the fact has been established that each species has characteristics more complex than we once imagined. Many of the dissociative phenomena are imperfectly understood at the present time, and in many instances, speculation as to their exact nature and significance has led to disagreement and contention. Much remains to be learned, and undoubtedly some of our present concepts will undergo revision. However, the subject is pregnant with possibilities,

and as investigations continue and our knowledge increases, it is probable that we shall gain a clearer concept of many of the now obscure problems of bacteriology." Part V, pages 143 to 334, is probably the part of greatest interest to bacteriologists and pathologists in general as it considers in systemic detail the bacteria of veterinary infections. Part VI describes the pathogenic fungi. This part lacks references to important articles on human infections caused by some of the organisms that are described. Part VII is devoted to protozoa. The chapter on parasitic protozoa is written by Col. Charles F. Craig, now professor of tropical medicine in Tulane University. Part VIII deals with the filtrable viruses of rabies, contagious pleuropneumonia, hog cholera, foot-and-mouth disease and other important animal diseases. In this part more references to recent work would have been of value. There is a short account of "pox virus," but no detailed description of cowpox or the production of vaccine virus for human use. The remaining four parts discuss serology, hematology, preparation of veterinary biologic products and bacteriologic examination of milk and water. The presentation is clear but somewhat labored and not concise or fluent. The continuous use of the scientific names of micro-organisms when simple and familiar names would answer the purpose fully gives a stilted, pedantic effect. The illustrations are helpful but only mediocre in quality. The book is recommendable as a reliable and comprehensive source of information in regard to the micro-organisms of veterinary infections.

Studies from the Institute for Medical Research, Federated Malay States; No. 21, Kuala Lumpur: Melioidosis. By A. T. Stanton, C.M.G., M.D., F.R.C.P., Chief Medical Adviser to the Secretary of State for the Colonies; formerly Director of Government Laboratories, F.M.S.; and William Fletcher, M.D., M.R.C.P., Member, Colonial Advisory Medical Committee; formerly Director, Institute for Medical Research, F.M.S. Pp. 59, with 37 figures. London: John Bale Sons & Danielsson, Ltd., 1932.

This report deals with the glanders-like disease (melioidosis, a disease like glanders), first described by Whitmore and Krishnaswamy in Rangoon in 1912. Cases have been observed in Burma, Malaya, French Indo-China and Ceylon. The disease occurs naturally in rats, rabbits, guinea-pigs, dogs and cats. In 1913 a severe outbreak occurred in laboratory animals at Kuala Pumpur. The causative organism, Bacillus whitmori, is "a member of the glanders group which possesses certain peculiar physical attributes, namely motility in young cultures and a corrugated appearance on glycerine-agar." The characteristic lesions are small, irregular areas of suppuration in various organs and tissues. B. whitmori is present in the lesions and may be found also in the blood, urine, sputum and arachnoid fluid. It is believed that the infection usually occurs by way of the digestive tract through contaminated food. There is no evidence of direct infection from man to man or from horse to man. The report gives a well illustrated and good account of the present knowledge of melioidosis in all its aspects.